Ending the STI Epidemic Through Prevention

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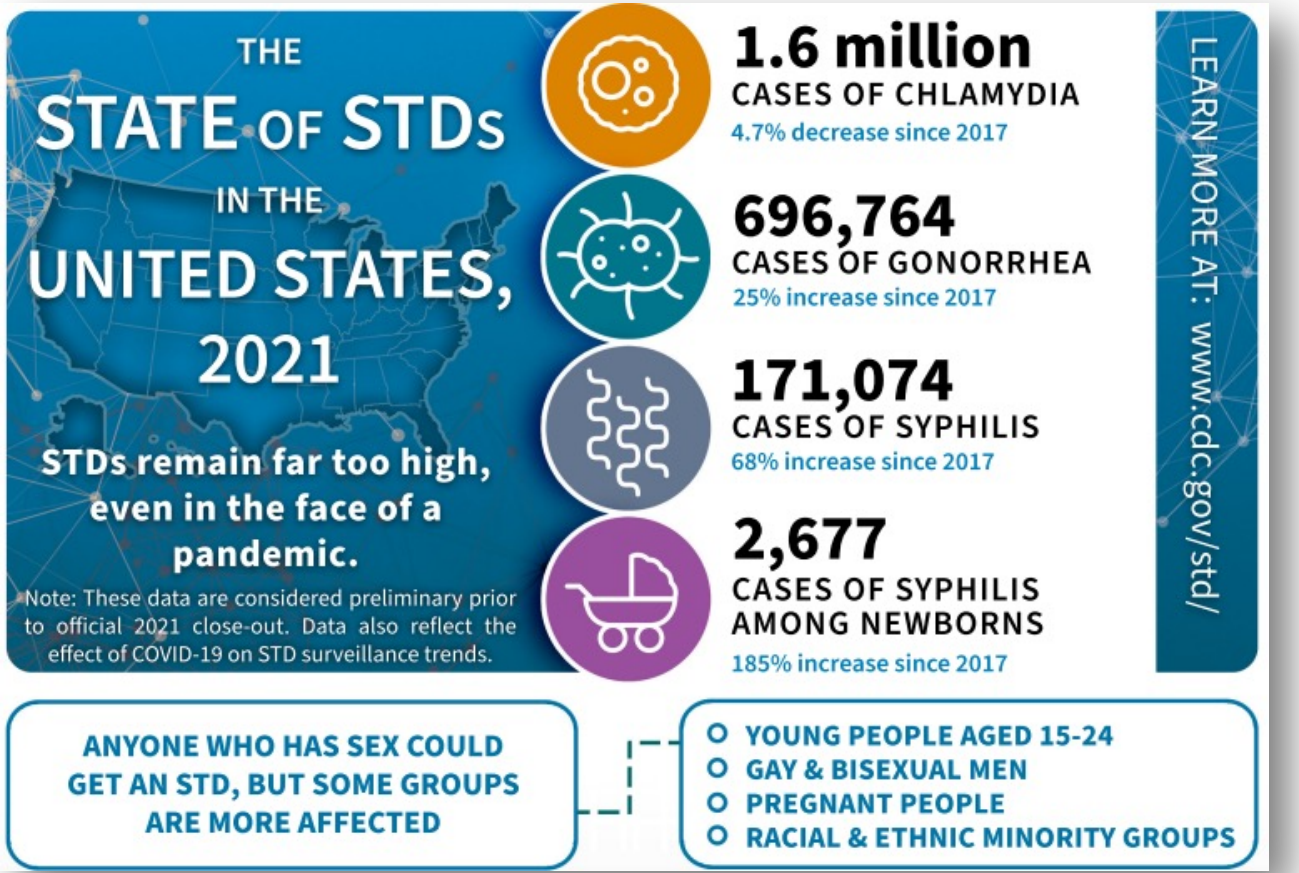
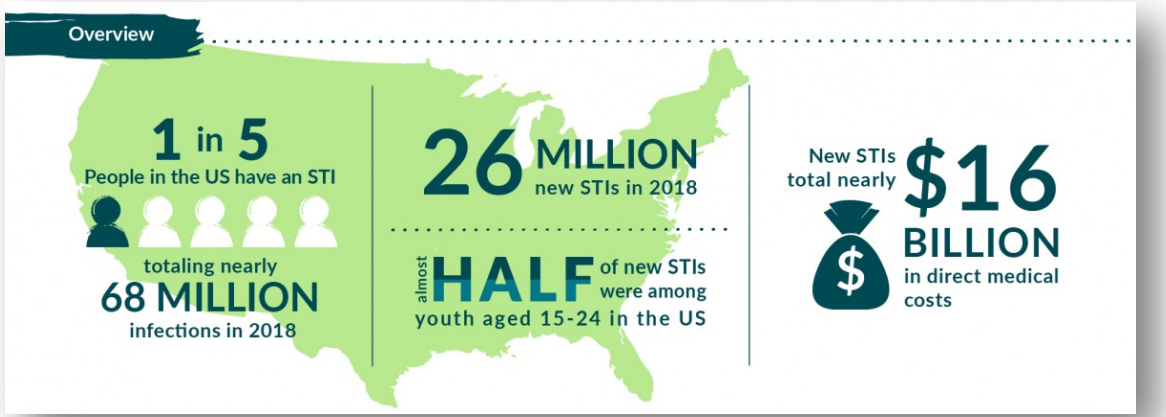
Objectives

1. Review the state of the STI Epidemic in the United States and New York City
2. Summarize the current landscape of STI prevention options
3. Appraise new methods for STI prevention
4. Discuss ongoing and upcoming STI prevention research at CUIMC

STIs Represent A Worsening Epidemic – In US

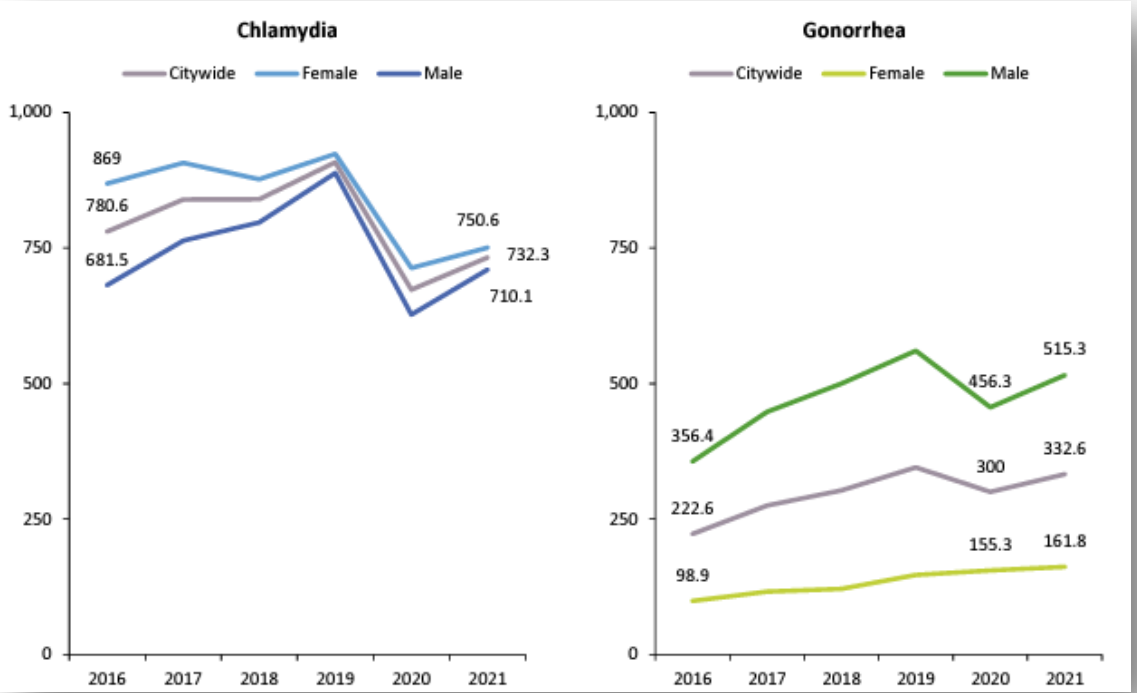




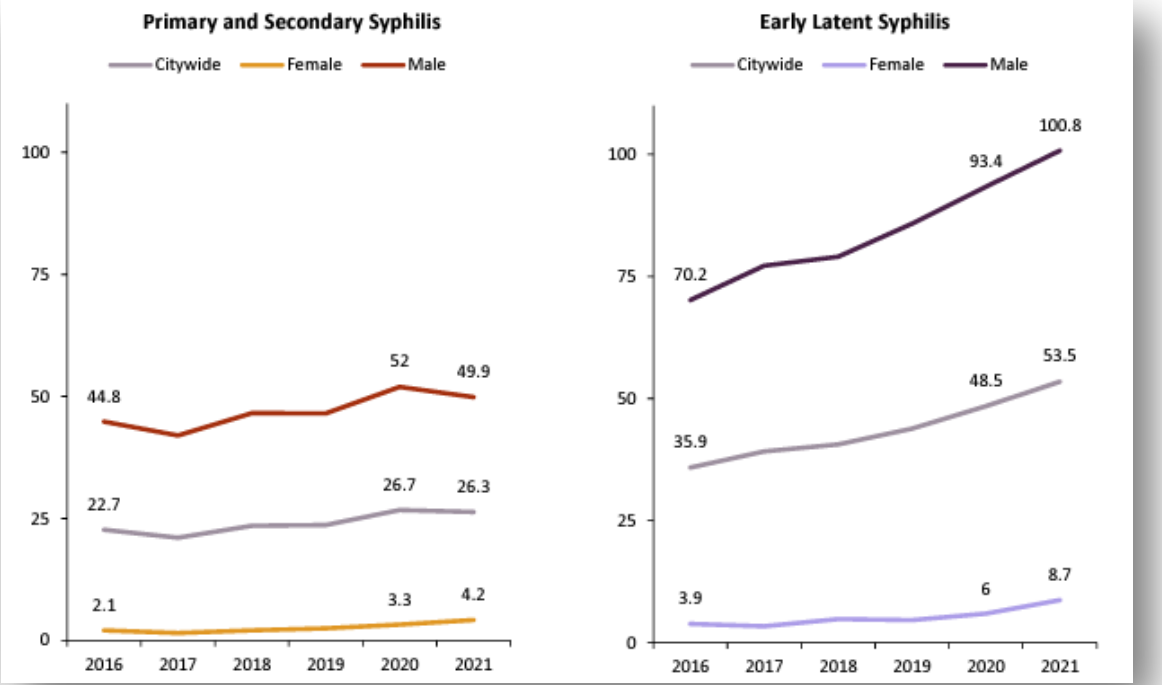
- https://www.cdc.gov/std/statistics/infographic.htm
- https://www.cdc.gov/std/statistics/2021/figures.htm

STIs Represent A Worsening Epidemic – In US

Gonorrhea and Chlamydia



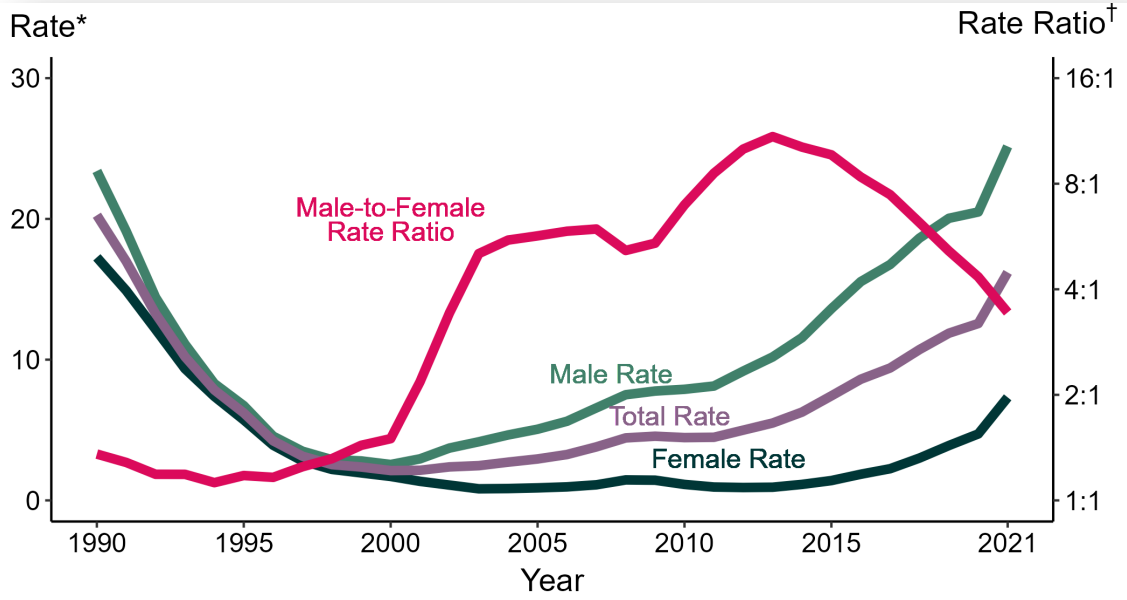
Syphilis



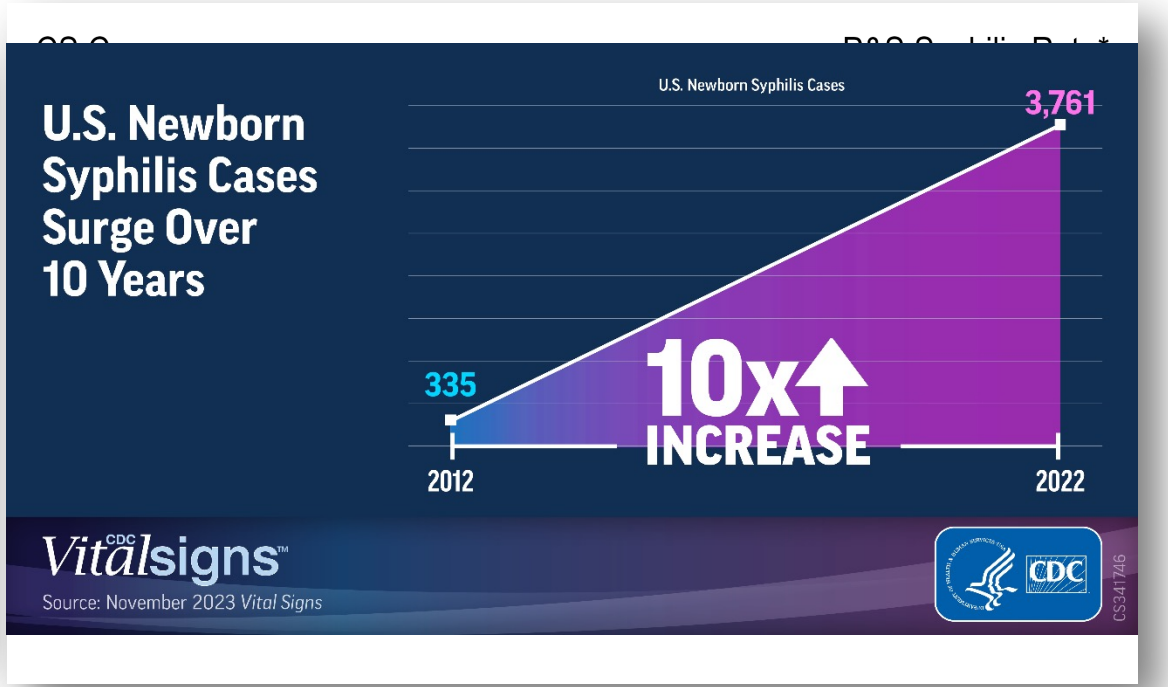
- https://www.nyc.gov/assets/doh/downloads/pdf/std/sti-2021-report.pdf

Why Do We Need to Prevent STIs?

Males to Female Ratio - Syphilis



Congenital Syphilis



- https://www.cdc. /std/statistics/2021/default.htm

Why Do We Need to Prevent STIs?

Rising Gonorrhea Resistance

The Commonwealth of Massachusetts
Executive Office of Health and Human Services
Department of Public Health
Bureau of Infectious Disease and Laboratory Sciences
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CLINICAL ALERT
January 19, 2023

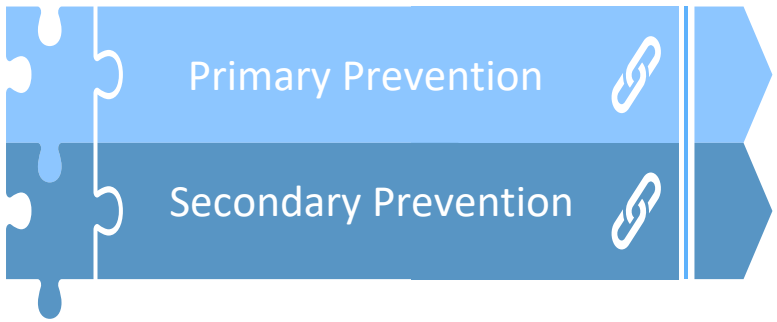
MULTI-DRUG NON-SUSCEPTIBLE GONORRHEA IN MASSACHUSETTS

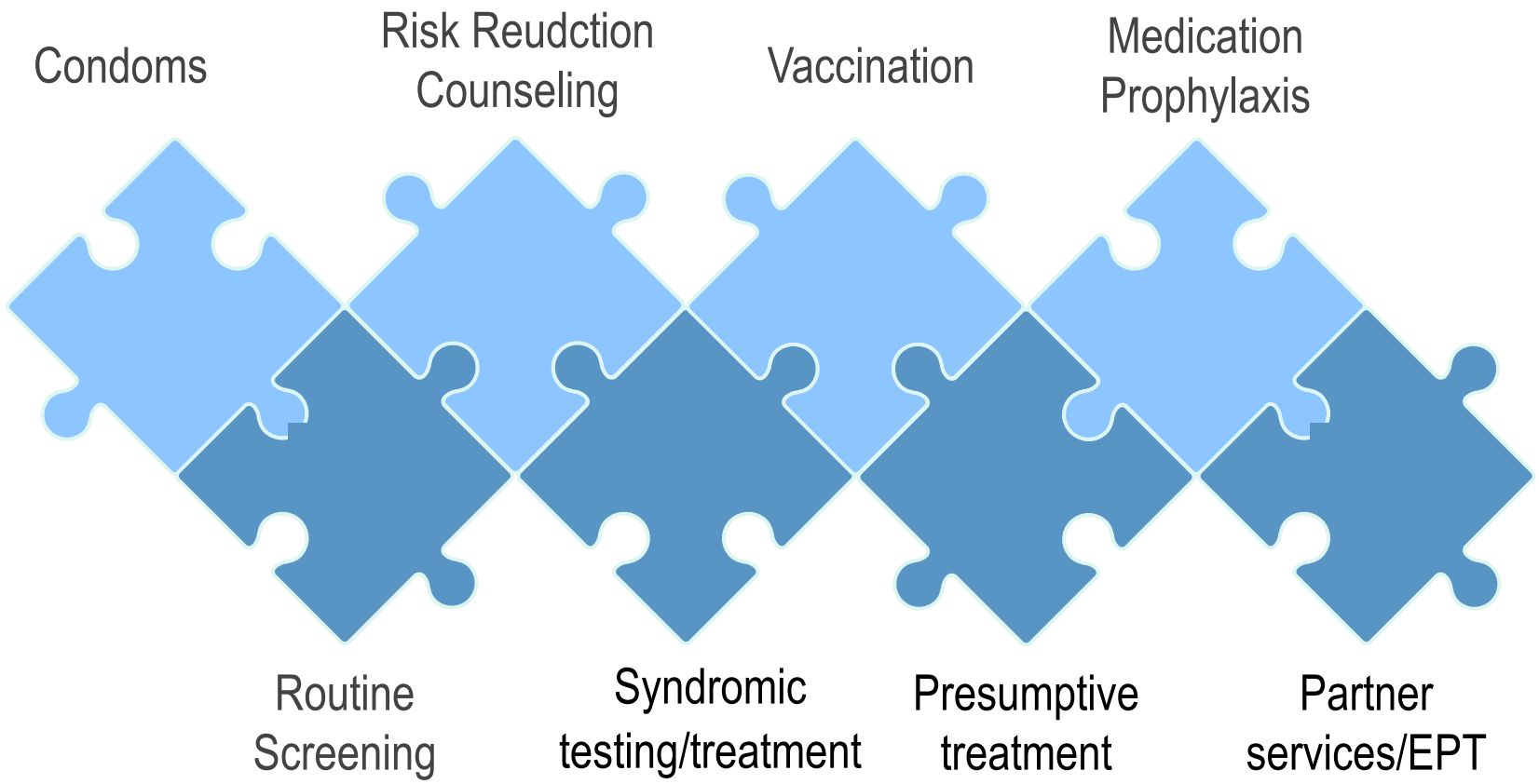
- A novel strain of multidrug-non-susceptible *Neisseria gonorrhoeae* with reduced susceptibility to ceftriaxone, cefixime, and azithromycin, and resistance to ciprofloxacin, penicillin, and tetracycline, has been identified in a Massachusetts resident. Although ceftriaxone 500 mg IM was effective at clearing infection for this case, this is the first isolate identified in the United States to demonstrate resistance or reduced susceptibility to all drugs that are recommended for treatment.
- Enhanced surveillance has identified a second isolate that, based on its genome, likely has similarly reduced susceptibility to ceftriaxone and cefixime.

STIs Are Not Benign

- Pelvic inflammatory disease
- Chronic pelvic pain
- Infertility
- Adverse pregnancy outcomes
  - Prematurity
  - Stillbirth
- Urethral strictures
- Gastrointestinal fistulas
- Peri-rectal abscesses
- Severe complications of syphilis
  - Permanent hearing or vision impairment

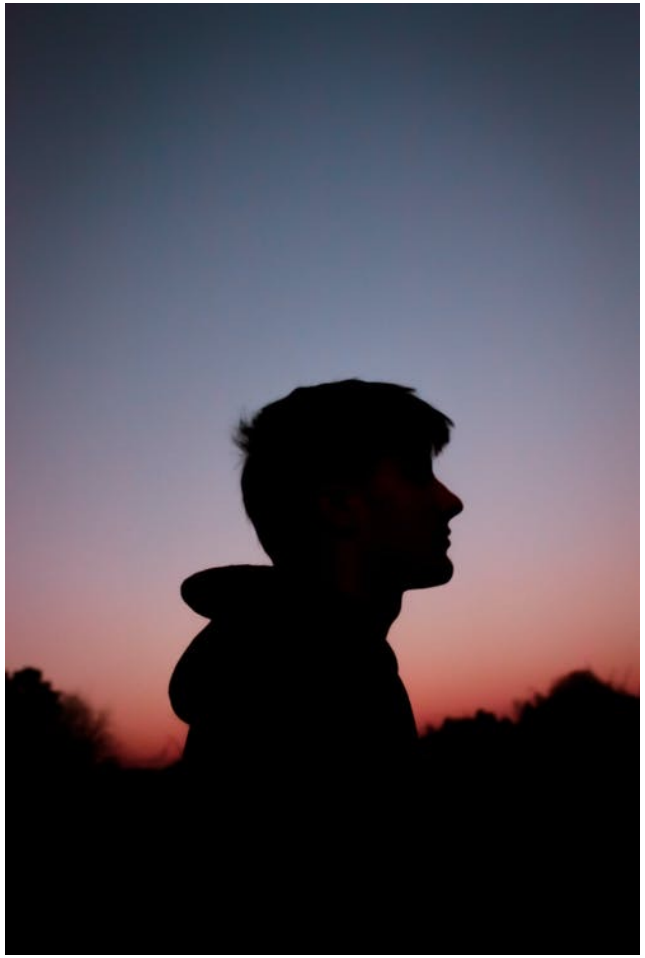
STI Prevention Landscape



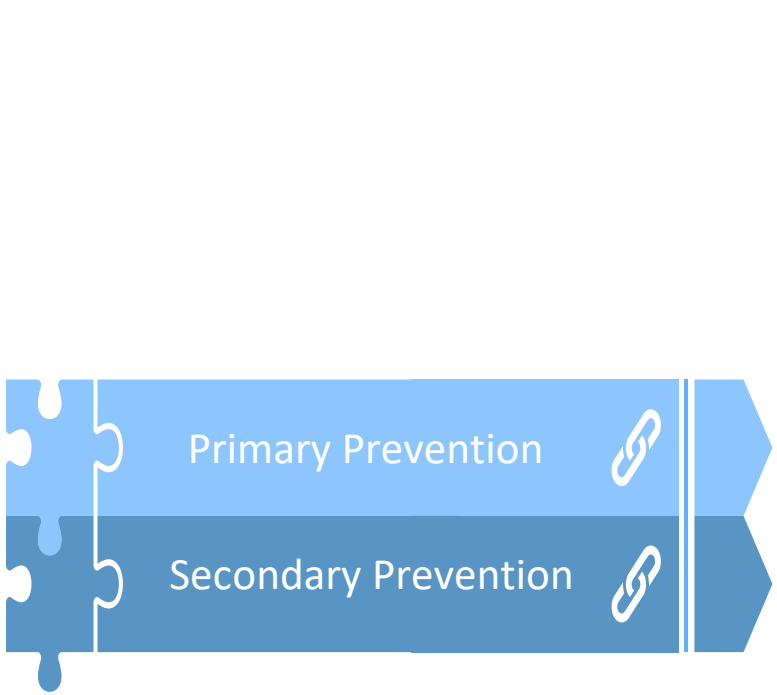


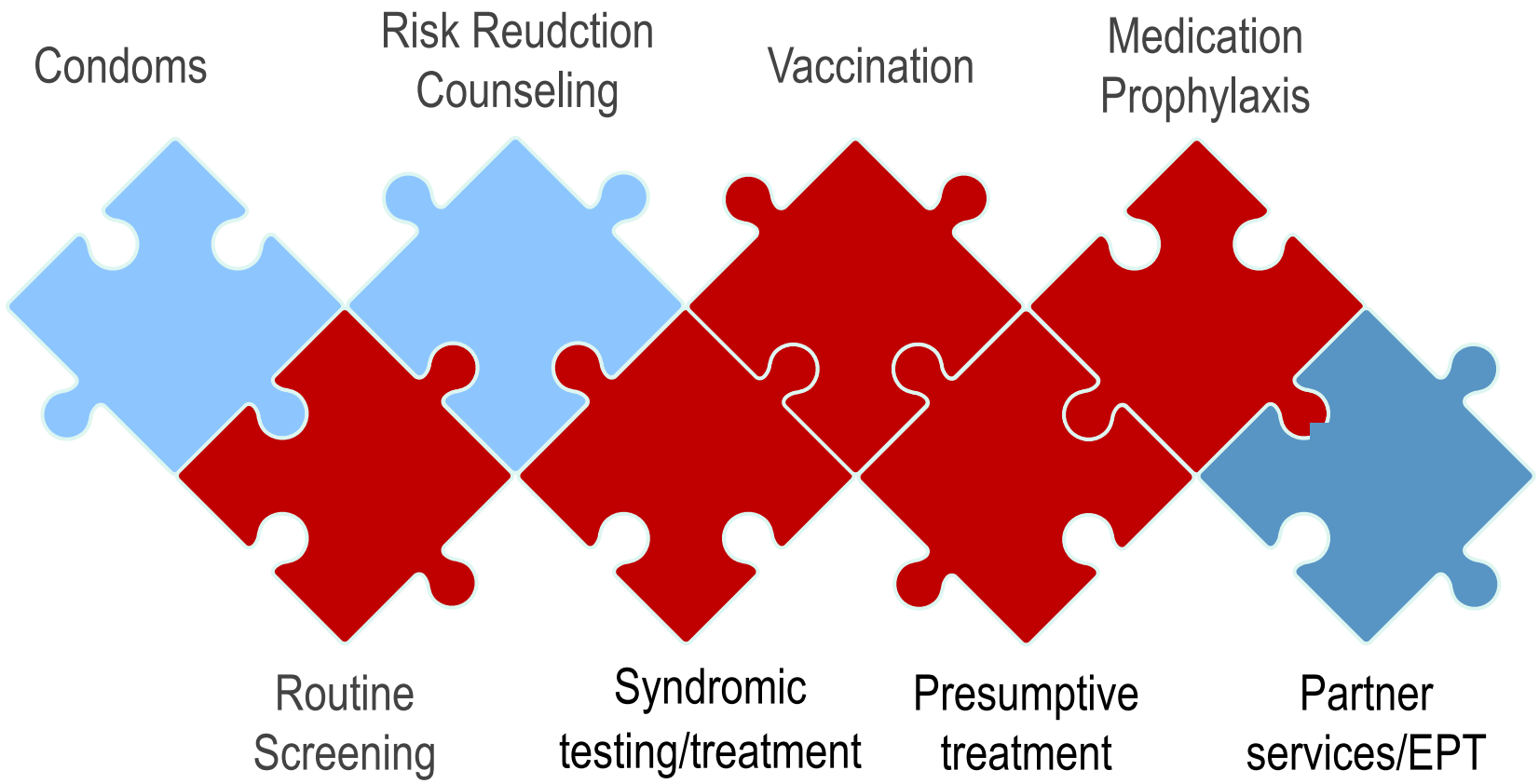
Meet Igor

- 29-year-old male in New York City
- Takes HIV PrEP for HIV prevention
- Sexually active with men
  - Four partners since his last visit, no condom usage
- Walks in to clinic due with 2 days of green penile discharge
- **Routine testing for HIV, syphilis, and three-site gonorrhea/chlamydia testing performed**
- **Treated empirically with Ceftriaxone and Doxycycline**



Igor's Prevention Plan





Igor's Prevention Plan

Primary Prevention

Vaccination

- HPV
- Hepatitis A/B
- Meningococcal ACYW
- Mpox

Medication

- HIV PrEP

Secondary Prevention

Routine screening

- Q3 Month Screening

Syndromic testing/treatment

Presumptive treatment

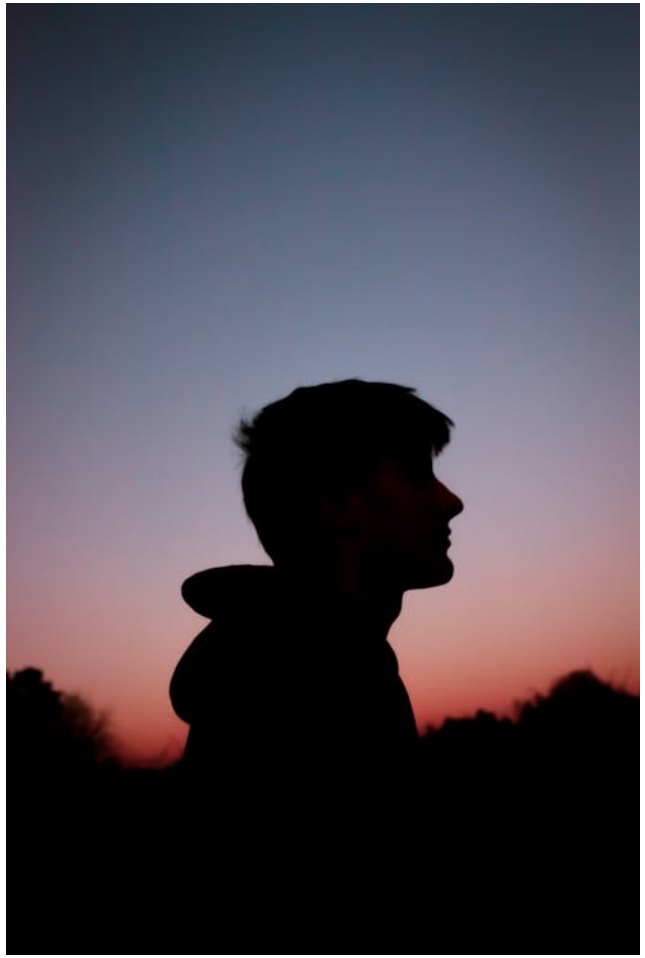
Igor's Results

Lab results:
HIV Ab/Ag - Negative
Urine GC/CT – GC positive
Pharyngeal GC/CT – GC positive
Rectal GC/CT – GC positive
RPR – 1:128 - 1:4 - 2 months ago

Received additional 7 days (total 14 days) of Doxycycline for early latent syphilis

Igor

- Returned 6 weeks later
- **“I got totally better but now it hurts again when I pee”**
  - Seven partners since his last visit
  - Is sure that his regular partners got treated for gonorrhea and syphilis
  - Repeat routine testing for HIV, syphilis, and three-site gonorrhea/chlamydia testing was performed
  - Treated empirically with Ceftriaxone and Doxycycline



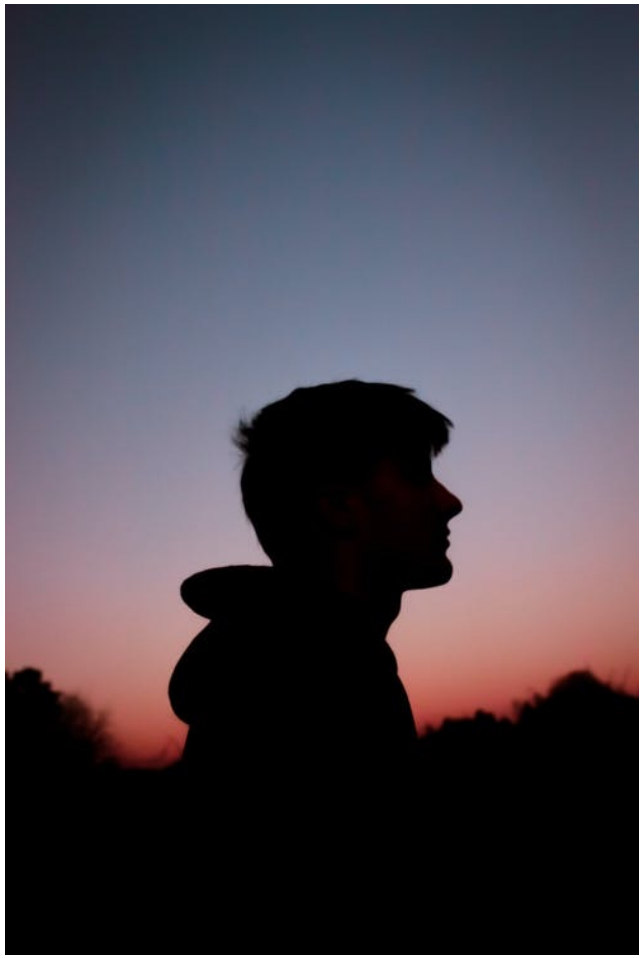
Igor's Results

Lab results:
HIV Ab/Ag - Negative
Urine GC/CT – GC positive
Pharyngeal GC/CT – GC positive
Rectal GC/CT – CT positive
RPR – 1:32 - 1:128 – 6 weeks ago

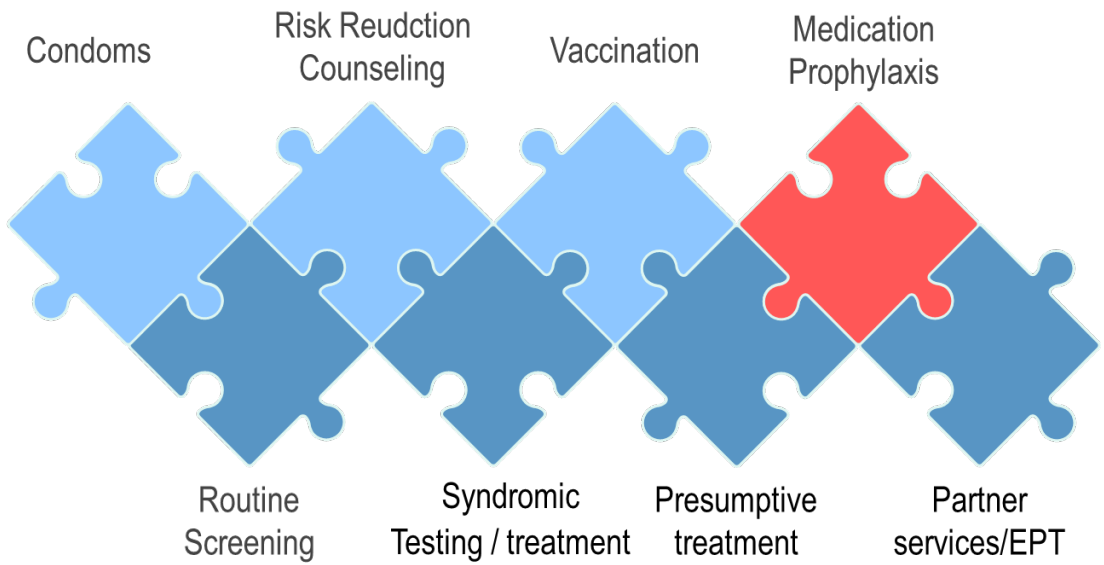
Igor

- Called to give Igor his results and he was pretty upset

- **“This is frustrating, is there anything I can do so I stop getting STIs?”**



Medication Prophylaxis



Medication Prophylaxis

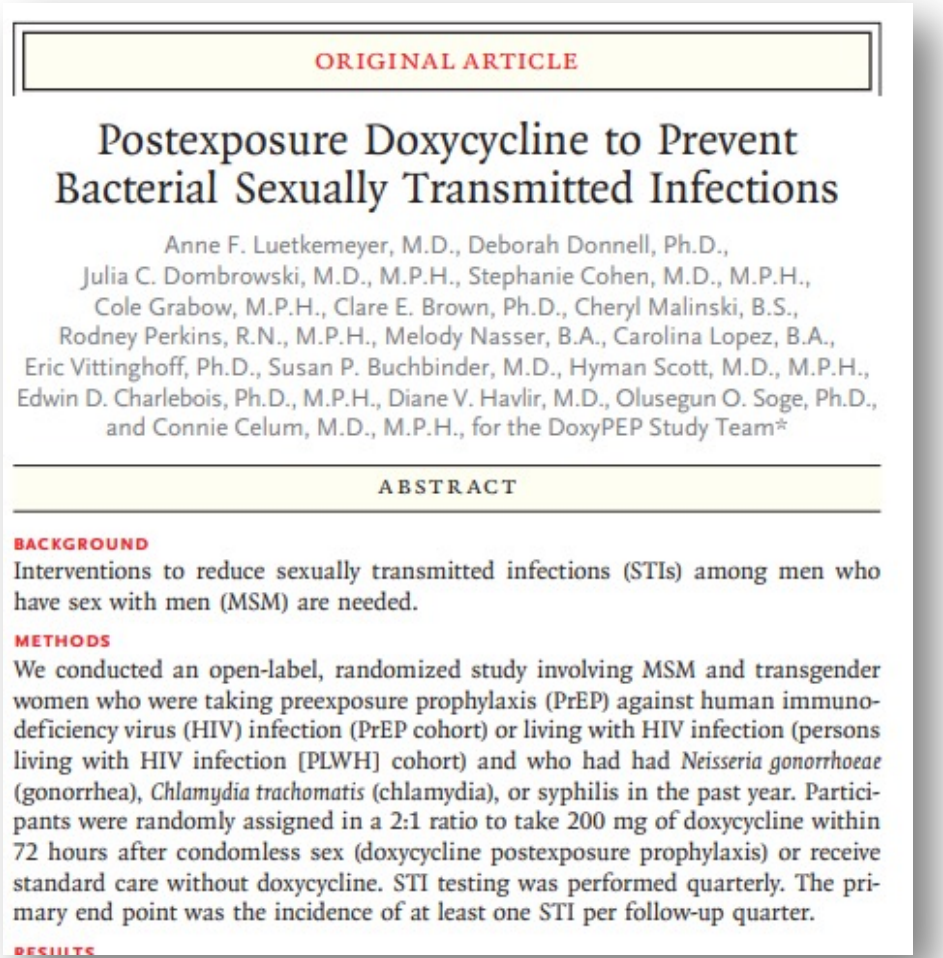
1. HIV post-exposure prophylaxis (PEP)
2. HIV pre-exposure prophylaxis (PrEP)
3. **Doxy-PEP**

What is Doxy-PEP?

- Doxycycline 200mg by mouth up to 72 hours after a condomless sexual encounter at any anatomic site

Does Doxy-PEP Prevent STIs?

Does Doxy-PEP Prevention STIs?



ORIGINAL ARTICLE

Postexposure Doxycycline to Prevent Bacterial Sexually Transmitted Infections

Anne F. Luetkemeyer, M.D., Deborah Donnell, Ph.D., Julia C. Dombrowski, M.D., M.P.H., Stephanie Cohen, M.D., M.P.H., Cole Grabow, M.P.H., Clare E. Brown, Ph.D., Cheryl Malinski, B.S., Rodney Perkins, R.N., M.P.H., Melody Nasser, B.A., Carolina Lopez, B.A., Eric Vittinghoff, Ph.D., Susan P. Buchbinder, M.D., Hyman Scott, M.D., M.P.H., Edwin D. Charlebois, Ph.D., M.P.H., Diane V. Havlir, M.D., Olusegun O. Soge, Ph.D., and Connie Celum, M.D., M.P.H., for the DoxyPEP Study Team*

ABSTRACT

BACKGROUND

Interventions to reduce sexually transmitted infections (STIs) among men who have sex with men (MSM) are needed.

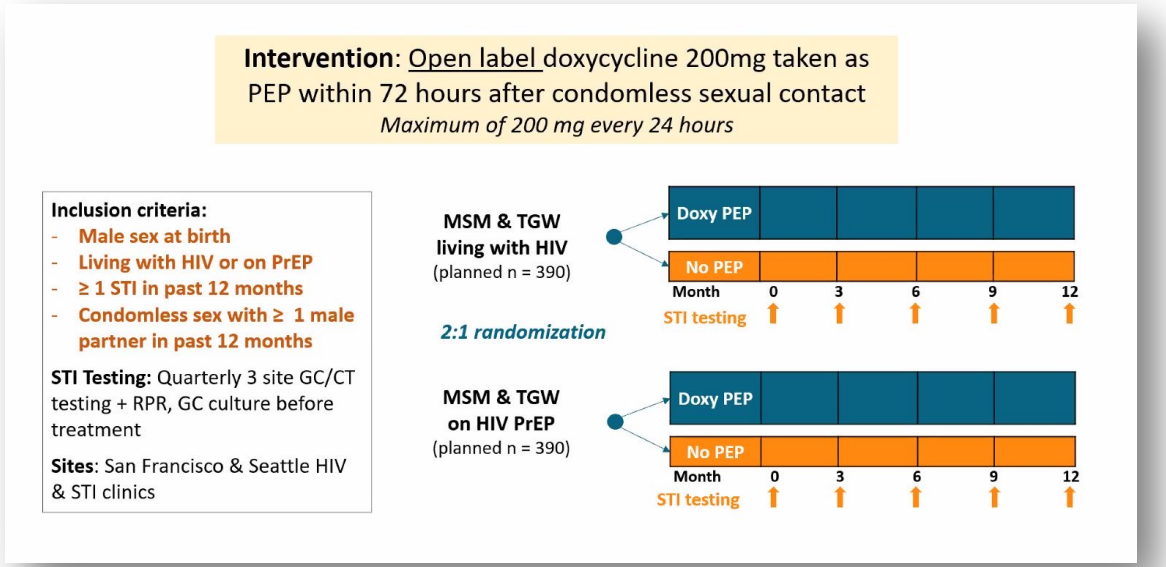
METHODS

We conducted an open-label, randomized study involving MSM and transgender women who were taking preexposure prophylaxis (PrEP) against human immunodeficiency virus (HIV) infection (PrEP cohort) or living with HIV infection (persons living with HIV infection [PLWH] cohort) and who had had *Neisseria gonorrhoeae* (gonorrhea), *Chlamydia trachomatis* (chlamydia), or syphilis in the past year. Participants were randomly assigned in a 2:1 ratio to take 200 mg of doxycycline within 72 hours after condomless sex (doxycycline postexposure prophylaxis) or receive standard care without doxycycline. STI testing was performed quarterly. The primary end point was the incidence of at least one STI per follow-up quarter.

RESULTS

• Luetkemeyer AF, Donnell D, Dombrowski JC, et al. Postexposure Doxycycline to Prevent Bacterial Sexually Transmitted Infections. N Engl J Med. 2023;388(14):1296-1306. doi:10.1056/NEJMoa2211934

DoxyPEP Trial

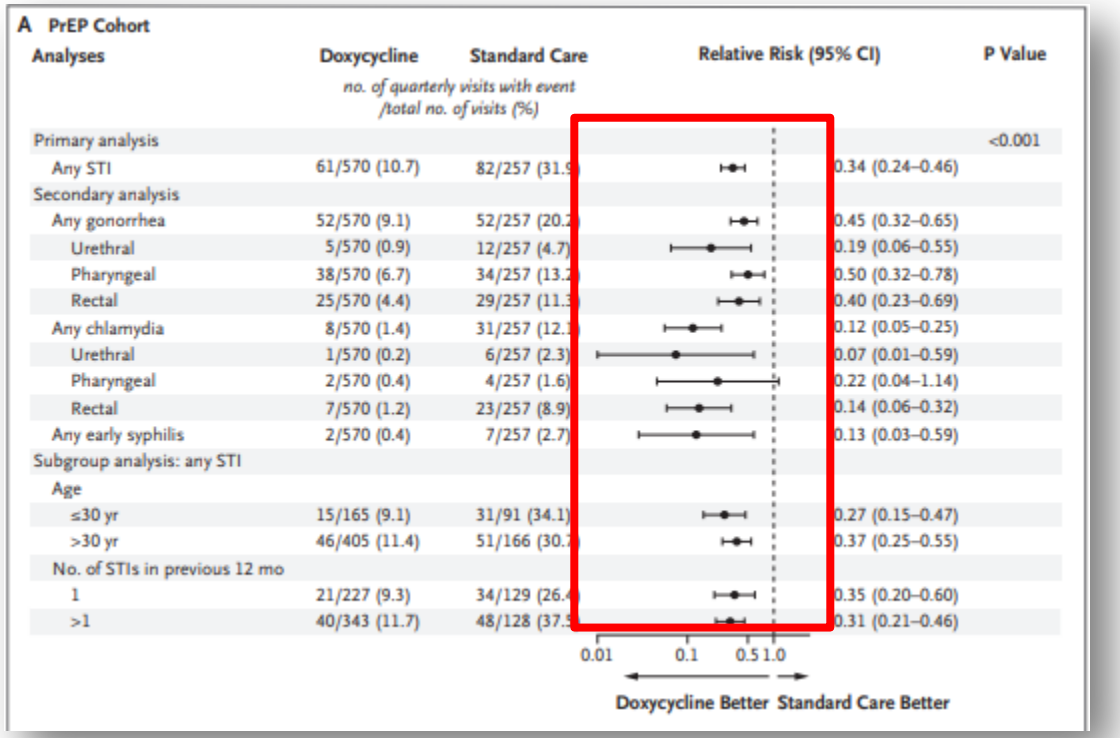


- **Design:** Multicenter, open-label, randomized, controlled, trial
- **Inclusion**
  - Men who have sex with men or Transgender women
  - Taking HIV PrEP or Living with HIV
  - Bacterial STI (chlamydia, gonorrhea, syphilis) in the past 12 months
  - Condomless sex with ≥ 1 male partner in past 12 months
- **Intervention**: 200 mg of doxycycline up to 72 hours after condomless sex
  - Max 200mg every 24 hours

Luetkemeyer AF, Donnell D, Dombrowski JC, et al. Postexposure Doxycycline to Prevent Bacterial Sexually Transmitted Infections. N Engl J Med. 2023;388(14):1296-1306. doi:10.1056/NEJMoa2211934

Doxy-PEP **Prevents** STIs

HIV PrEP Cohort



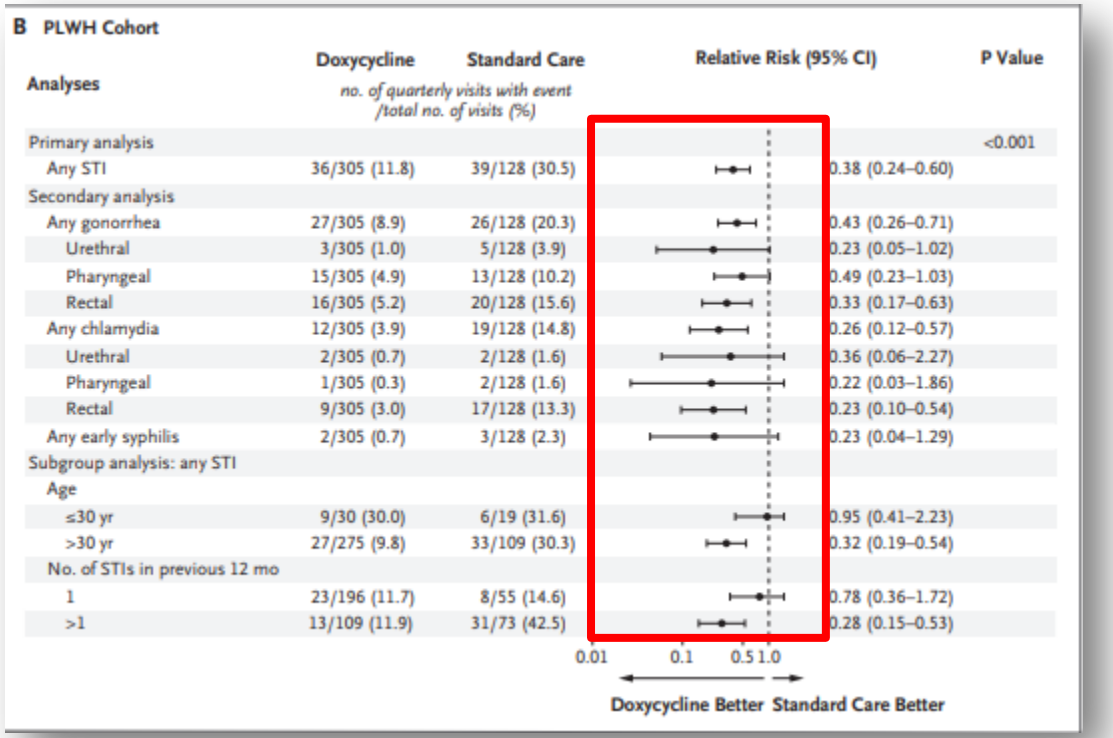
A PrEP Cohort

Analyses	Doxycycline (no. of quarterly visits with event /total no. of visits (%))	Standard Care (no. of quarterly visits with event /total no. of visits (%))	Relative Risk (95% CI)	P Value
Primary analysis				<0.001
Any STI	61/570 (10.7)	82/257 (31.9)	0.34 (0.24–0.46)	
Secondary analysis				
Any gonorrhea	52/570 (9.1)	52/257 (20.2)	0.45 (0.32–0.65)	
Urethral	5/570 (0.9)	12/257 (4.7)	0.19 (0.06–0.55)	
Pharyngeal	38/570 (6.7)	34/257 (13.2)	0.50 (0.32–0.78)	
Rectal	25/570 (4.4)	29/257 (11.3)	0.40 (0.23–0.69)	
Any chlamydia	8/570 (1.4)	31/257 (12.1)	0.12 (0.05–0.25)	
Urethral	1/570 (0.2)	6/257 (2.3)	0.07 (0.01–0.59)	
Pharyngeal	2/570 (0.4)	4/257 (1.6)	0.22 (0.04–1.14)	
Rectal	7/570 (1.2)	23/257 (8.9)	0.14 (0.06–0.32)	
Any early syphilis	2/570 (0.4)	7/257 (2.7)	0.13 (0.03–0.59)	
Subgroup analysis: any STI				
Age				
≤30 yr	15/165 (9.1)	31/91 (34.1)	0.27 (0.15–0.47)	
>30 yr	46/405 (11.4)	51/166 (30.7)	0.37 (0.25–0.55)	
No. of STIs in previous 12 mo				
1	21/227 (9.3)	34/129 (26.4)	0.35 (0.20–0.60)	
>1	40/343 (11.7)	48/128 (37.5)	0.31 (0.21–0.46)	

0.01 0.1 0.5 1.0

Doxycycline Better Standard Care Better

PWH Cohort



B PLWH Cohort

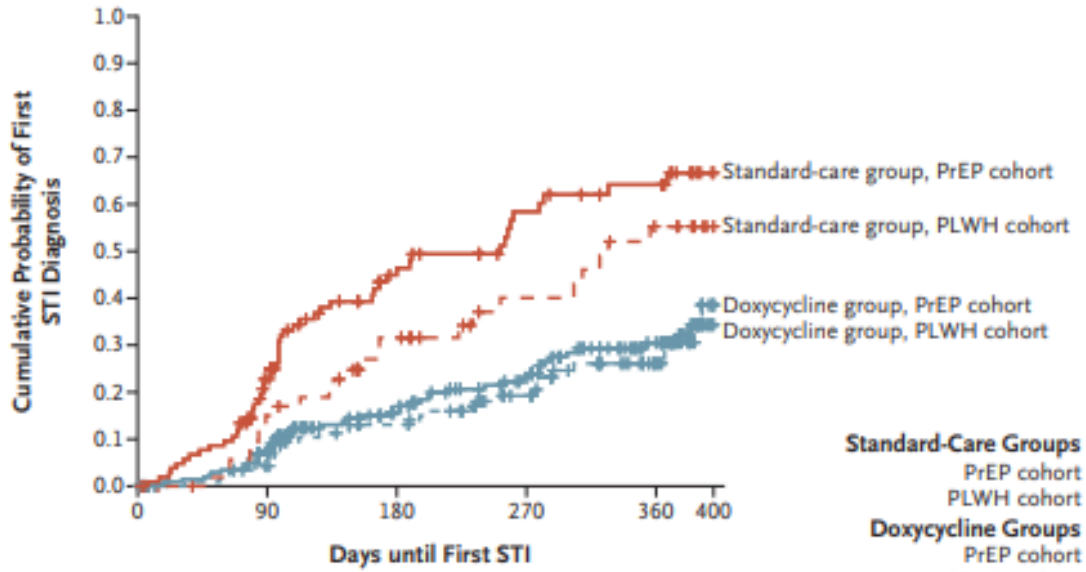
Analyses	Doxycycline (no. of quarterly visits with event /total no. of visits (%))	Standard Care (no. of quarterly visits with event /total no. of visits (%))	Relative Risk (95% CI)	P Value
Primary analysis				<0.001
Any STI	36/305 (11.8)	39/128 (30.5)	0.38 (0.24–0.60)	
Secondary analysis				
Any gonorrhea	27/305 (8.9)	26/128 (20.3)	0.43 (0.26–0.71)	
Urethral	3/305 (1.0)	5/128 (3.9)	0.23 (0.05–1.02)	
Pharyngeal	15/305 (4.9)	13/128 (10.2)	0.49 (0.23–1.03)	
Rectal	16/305 (5.2)	20/128 (15.6)	0.33 (0.17–0.63)	
Any chlamydia	12/305 (3.9)	19/128 (14.8)	0.26 (0.12–0.57)	
Urethral	2/305 (0.7)	2/128 (1.6)	0.36 (0.06–2.27)	
Pharyngeal	1/305 (0.3)	2/128 (1.6)	0.22 (0.03–1.86)	
Rectal	9/305 (3.0)	17/128 (13.3)	0.23 (0.10–0.54)	
Any early syphilis	2/305 (0.7)	3/128 (2.3)	0.23 (0.04–1.29)	
Subgroup analysis: any STI				
Age				
≤30 yr	9/30 (30.0)	6/19 (31.6)	0.95 (0.41–2.23)	
>30 yr	27/275 (9.8)	33/109 (30.3)	0.32 (0.19–0.54)	
No. of STIs in previous 12 mo				
1	23/196 (11.7)	8/55 (14.6)	0.78 (0.36–1.72)	
>1	13/109 (11.9)	31/73 (42.5)	0.28 (0.15–0.53)	

0.01 0.1 0.5 1.0

Doxycycline Better Standard Care Better

• Luetkemeyer AF, Donnell D, Dombrowski JC, et al. Postexposure Doxycycline to Prevent Bacterial Sexually Transmitted Infections. N Engl J Med. 2023;388(14):1296-1306. doi:10.1056/NEJMoa2211934

Doxy-PEP **Prevents** STIs



No. at Risk					
Standard-care groups					
PrEP cohort	107	72	37	23	17
PLWH cohort	55	45	30	20	13
Doxycycline groups					
PrEP cohort	220	179	122	93	57
PLWH cohort	119	111	91	64	36

	No. of Events/ No. of Participants
Standard-Care Groups	
PrEP cohort	53/107
PLWH cohort	24/55
Doxycycline Groups	
PrEP cohort	51/220
PLWH cohort	30/119

Hazard ratio for PrEP cohort, 0.34 (95% CI, 0.23–0.51)

Hazard ratio for PLWH cohort, 0.48 (95% CI, 0.28–0.83)

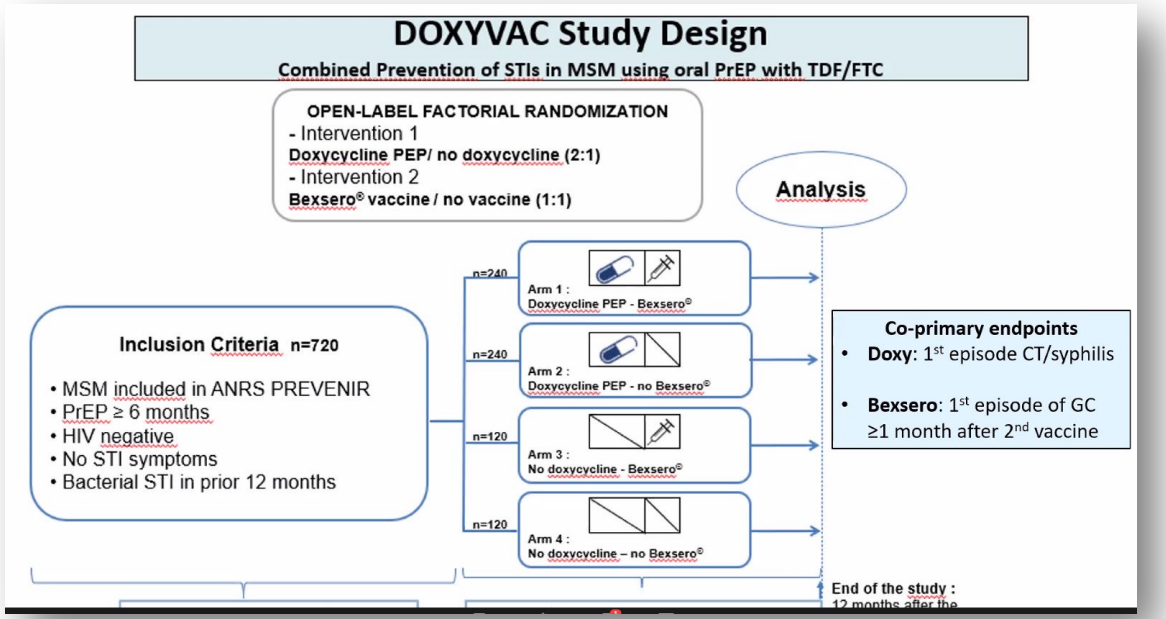
Figure 3. Kaplan–Meier Estimate of Time to First STI Diagnosis.

The cumulative probability of any incident bacterial STI (chlamydia, gonorrhea, or syphilis) is shown according to study group (doxycycline and standard care) and participant cohort (PrEP and PLWH).

- The combined incidence of gonorrhea, chlamydia, and syphilis was **lower by two thirds (65%)** with Doxy-PEP than with standard care

- Luetkemeyer AF, Donnell D, Dombrowski JC, et al. Postexposure Doxycycline to Prevent Bacterial Sexually Transmitted Infections. N Engl J Med. 2023;388(14):1296-1306. doi:10.1056/NEJMoa2211934

DoxyVac Trial



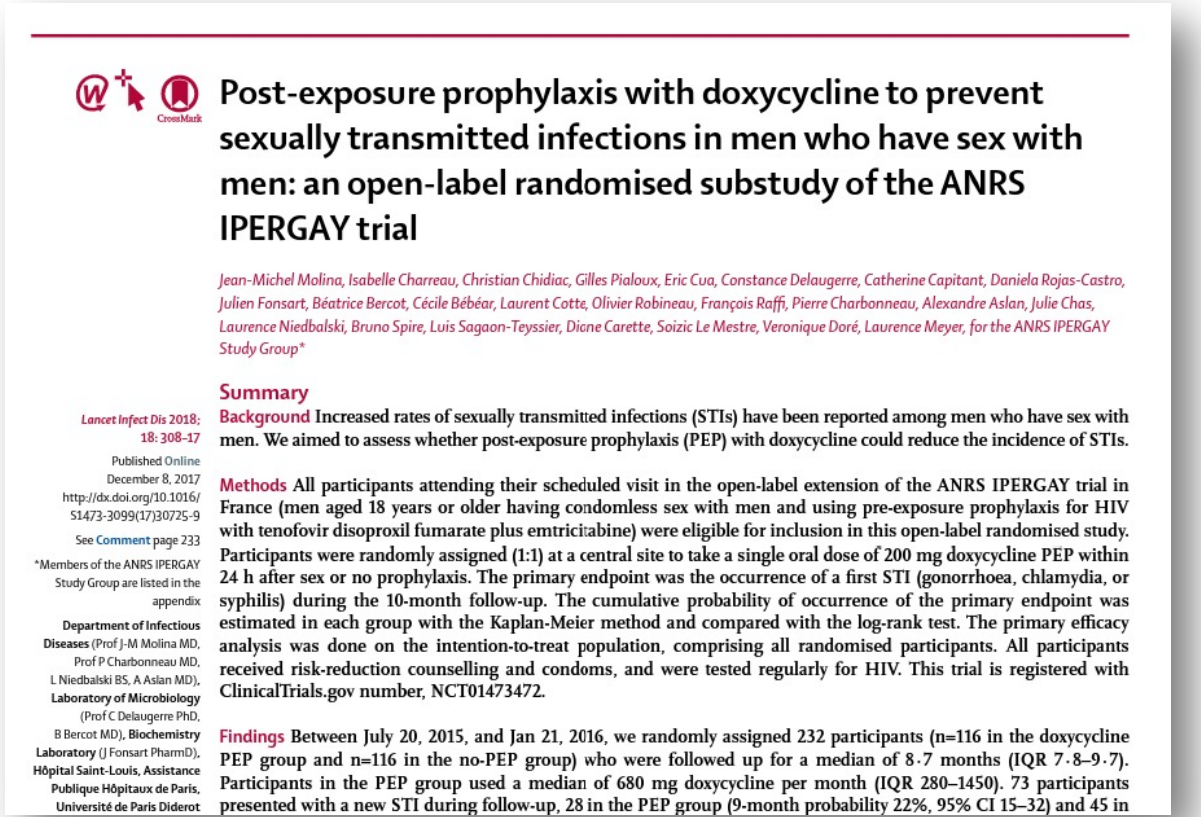
- **Design:** Multicenter, **2x2 factorial**, open-label, randomized, controlled, trial

- **Inclusion:**
  - MSM on PrEP > 6 months
  - Enrolled in ANRS Prevenir Study
  - Bacterial STI in prior 12 months
  - **No STI symptoms**

- **Intervention**: 200 mg of doxycycline up to 72 hours after condomless sex
  - Max 200mg every 24 hours

1. Molina et al DOXYVAC CROI 2023 Abstract 119
2. Liu AY, Buchbinder SP. CROI 2023: Epidemiologic Trends and Prevention for HIV and Other Sexually Transmitted Infections. Top Antivir Med. 2023;31(3):468-492.

IPERGAY Trial



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, Dione Carette, Soizic Le Mestre, Veronique Doré, Laurence Meyer, for the ANRS IPERGAY Study Group**

Lancet Infect Dis 2018; 18: 308–17

Published Online December 8, 2017 http://dx.doi.org/10.1016/S1473-3099(17)30725-9

See Comment page 233

*Members of the ANRS IPERGAY Study Group are listed in the appendix

Department of Infectious Diseases (Prof J-M Molina MD, Prof P Charbonneau MD, L Niedbalski BS, A Aslan MD), **Laboratory of Microbiology** (Prof C Delaugerre PhD, B Bercot MD), **Biochemistry Laboratory** (J Fonsart PharmD), **Hôpital Saint-Louis, Assistance Publique Hôpitaux de Paris, Université de Paris Diderot**

Summary

Background Increased rates of sexually transmitted infections (STIs) have been reported among men who have sex with men. We aimed to assess whether post-exposure prophylaxis (PEP) with doxycycline could reduce the incidence of STIs.

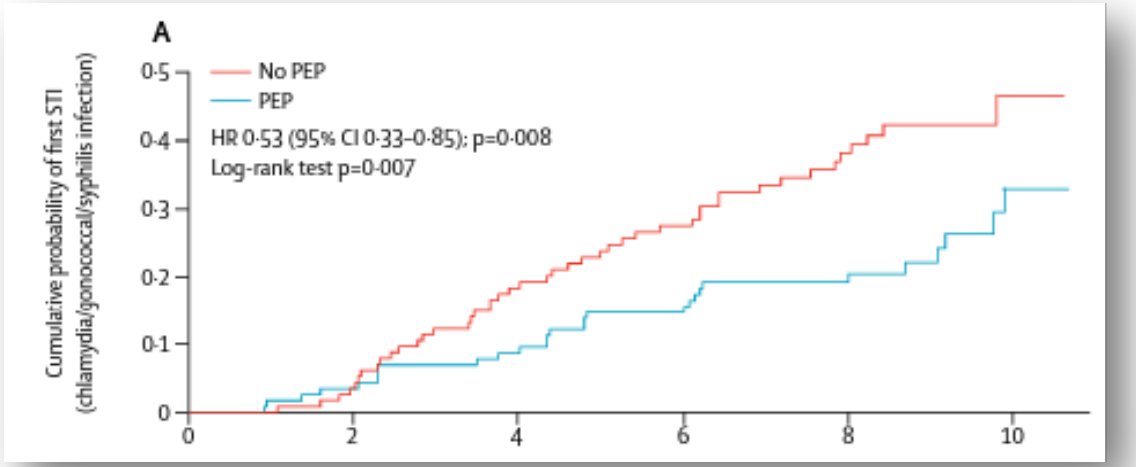
Methods All participants attending their scheduled visit in the open-label extension of the ANRS IPERGAY trial in France (men aged 18 years or older having condomless sex with men and using pre-exposure prophylaxis for HIV with tenofovir disoproxil fumarate plus emtricitabine) were eligible for inclusion in this open-label randomised study. Participants were randomly assigned (1:1) at a central site to take a single oral dose of 200 mg doxycycline PEP within 24 h after sex or no prophylaxis. The primary endpoint was the occurrence of a first STI (gonorrhoea, chlamydia, or syphilis) during the 10-month follow-up. The cumulative probability of occurrence of the primary endpoint was estimated in each group with the Kaplan-Meier method and compared with the log-rank test. The primary efficacy analysis was done on the intention-to-treat population, comprising all randomised participants. All participants received risk-reduction counselling and condoms, and were tested regularly for HIV. This trial is registered with ClinicalTrials.gov number, NCT01473472.

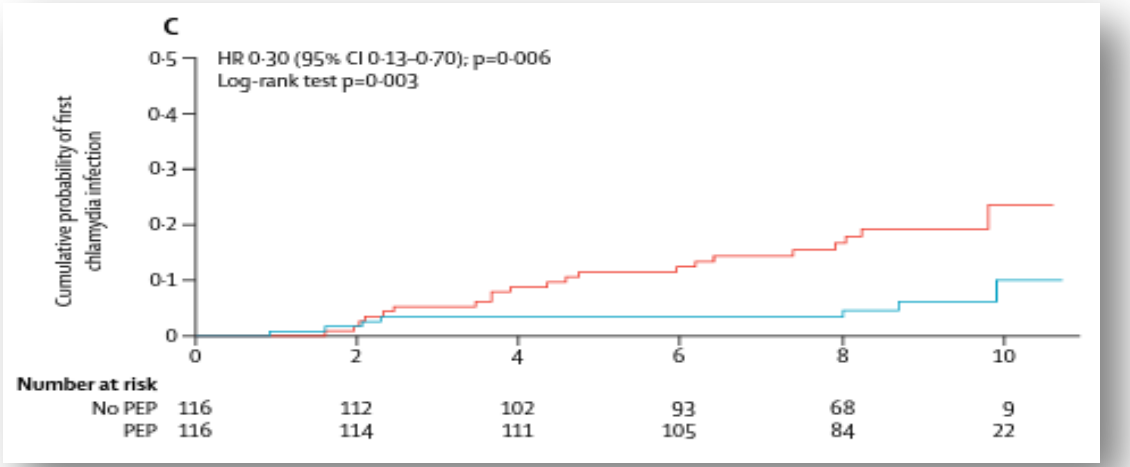
Findings Between July 20, 2015, and Jan 21, 2016, we randomly assigned 232 participants (n=116 in the doxycycline PEP group and n=116 in the no-PEP group) who were followed up for a median of 8·7 months (IQR 7·8–9·7). Participants in the PEP group used a median of 680 mg doxycycline per month (IQR 280–1450). 73 participants presented with a new STI during follow-up, 28 in the PEP group (9-month probability 22%, 95% CI 15–32) and 45 in

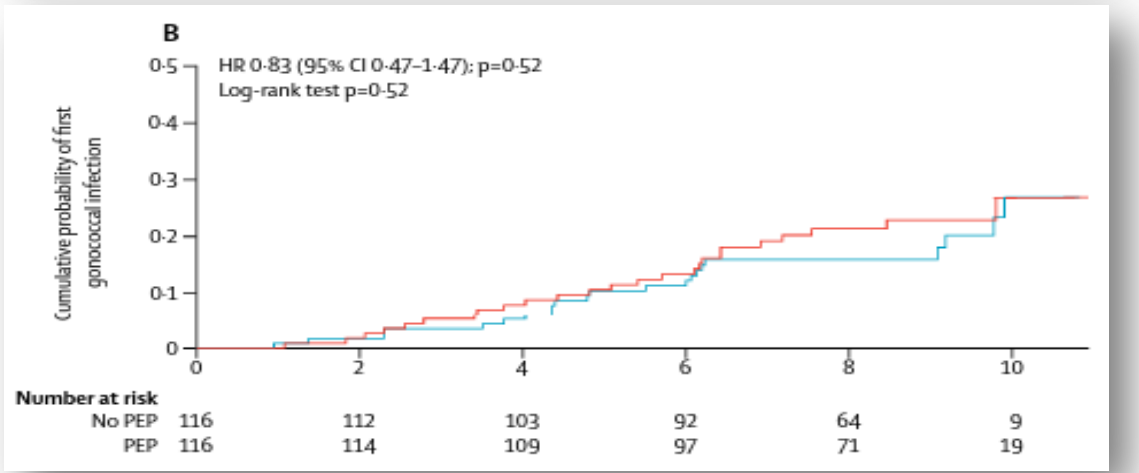
- **Design:** Multicenter, open-label, randomized, controlled, trial
- **Inclusion:**
  - MSM on PrEP (age >18)
  - Enrolled in ANRS IPERGAY Study
  - Condomless sex with men
- **Intervention**: 200 mg of doxycycline up to 72 hours after condomless sex

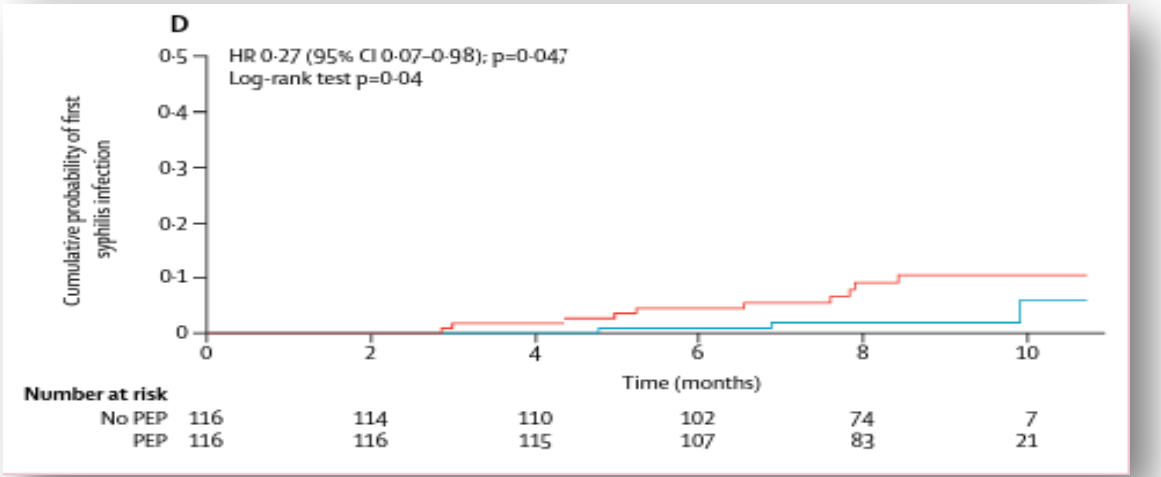
Molina JM, Charreau I, Chidiac C, et al. Post-exposure prophylaxis with doxycycline to prevent sexually transmitted infections in men who have sex with men: an open-label randomised substudy of the ANRS IPERGAY trial. Lancet Infect Dis. 2018;18(3):308-317. doi:10.1016/S1473-3099(17)30725-9

Doxy-PEP **Prevents** Chlamydia and Syphilis









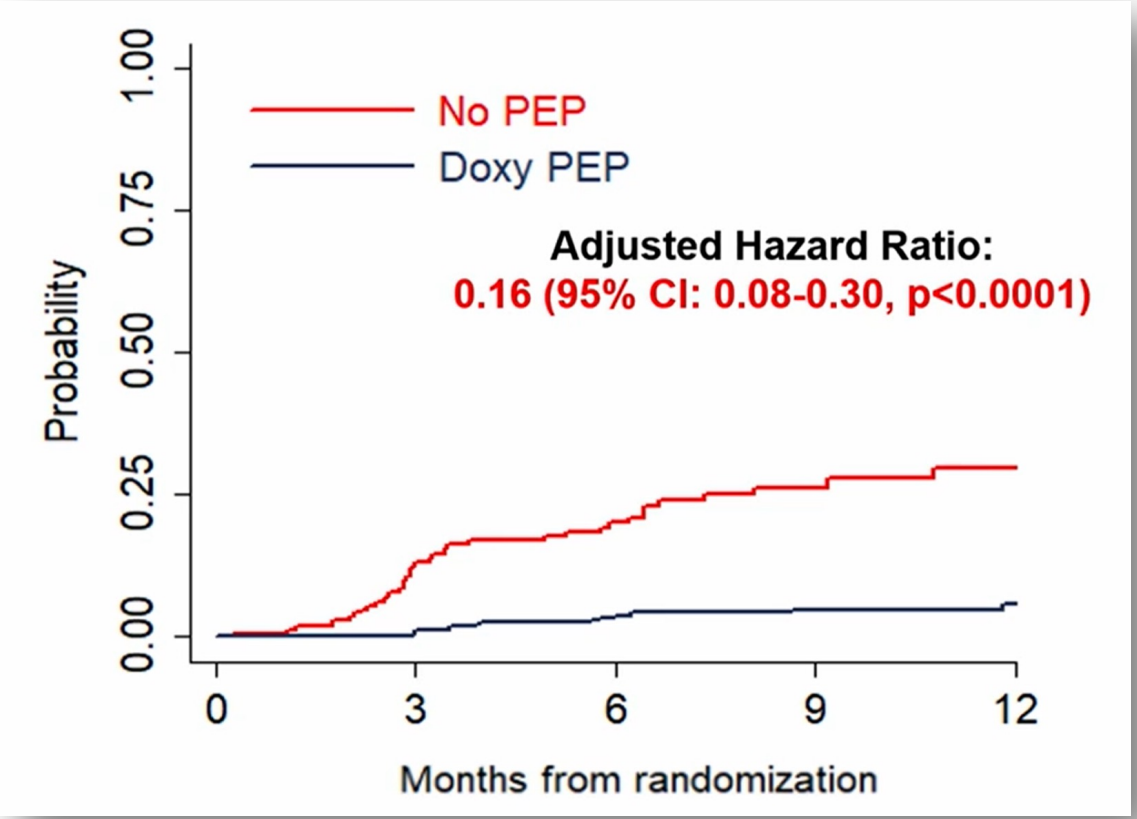
COLUMBIA | COLUMBIA UNIVERSITY IRVING MEDICAL CENTER

- Molina JM, Charreau I, Chidiac C, et al. 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. Lancet Infect Dis. 2018;18(3):308-317. doi:10.1016/S1473-3099(17)30725-9

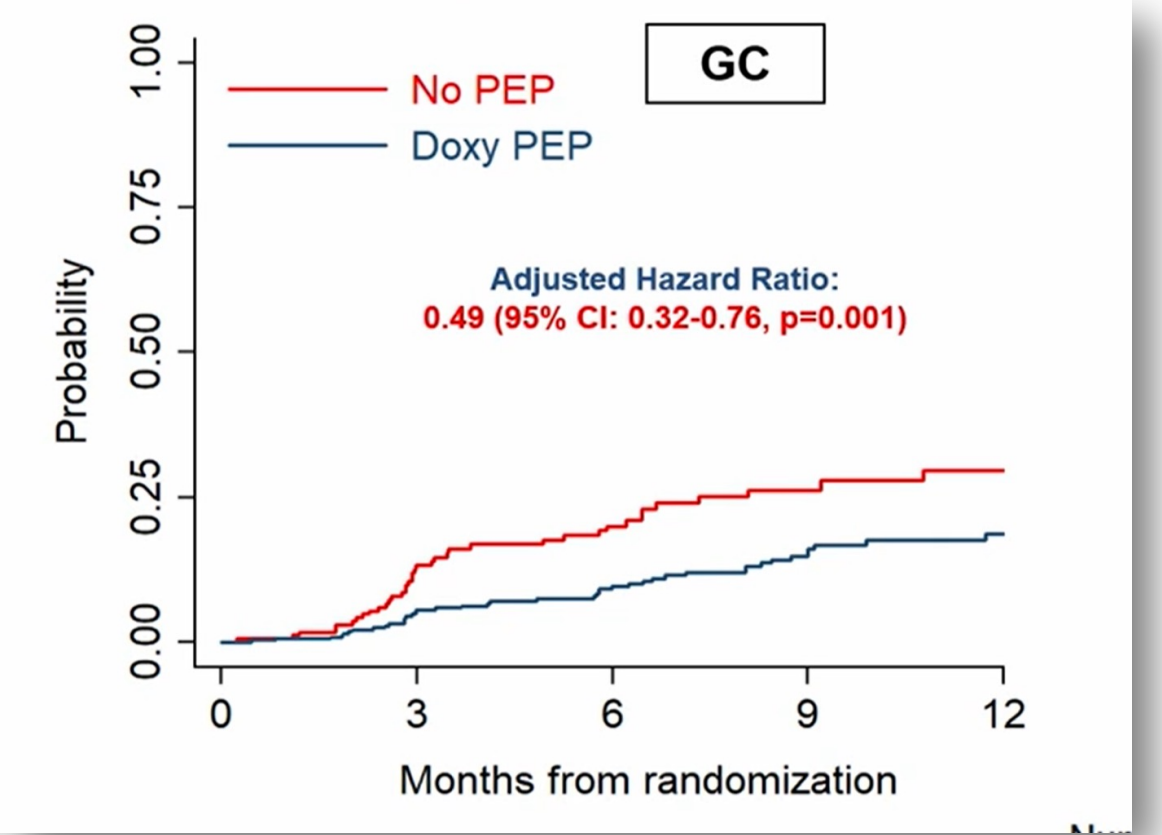
NEW YORK CITY STD HIV PREVENTION TRAINING CENTER

DoxyPEP **Prevents** STIs in DoxyVac

Time to First CT/Syphilis



Time to First GC



- Molina et al DOXYVAC CROI 2023 Abstract 119
- Liu AY, Buchbinder SP. CROI 2023: Epidemiologic Trends and Prevention for HIV and Other Sexually Transmitted Infections. Top Antivir Med. 2023;31(3):468-492.

dPEP Trial - Does Doxy-PEP Work in Women?

STUDY PROTOCOL Open Access

Doxycycline post-exposure prophylaxis for prevention of sexually transmitted infections among Kenyan women using HIV pre-exposure prophylaxis: study protocol for an open-label randomized trial

Jenell Stewart[1,2*], Elizabeth Bukusi[1,3], Fredericka A. Sesay[1,4], Kevin Oware[3], Deborah Donnell[1,5], Olusegun O. Soge[1,2,6], Connie Celum[1,2,4], Josephine Odoyo[3], Zachary A. Kwena[3], Caitlin W. Scoville[1], Lauren R. Violette[2,4], Susan Morrison[1], Jane Simoni[7], R. Scott McClelland[1,2,4], Ruanne Barnabas[1,2,4], Monica Gandhi[8] and Jared M. Baeten[1,2,4]

- **Design:** Open-label, randomized, controlled, trial
- **Inclusion**
  - Cis-gender women
  - Age 18-30
  - Has a current prescription for PrEP
- **Intervention:** 200 mg of doxycycline within 72 hours after condomless sex

- Stewart et al DOXYVAC CROI 2023 Abstract 121
- Oware K, Adiema L, Rono B, et al. Characteristics of Kenyan women using HIV PrEP enrolled in a randomized trial on doxycycline postexposure prophylaxis for sexually transmitted infection prevention. BMC Womens Health. 2023;23(1):296. Published 2023 Jun 3. doi:10.1186/s12905-023-02413-0

Doxy-PEP **Did Not** Prevent STIs in Females

- Overall STI incidence was 27 per 100 person-years
- Women assigned to doxy-PEP reported coverage of 78% of sex acts
- 109 incident STI events detected:
  - 50 in the doxy-PEP arm
  - 59 in the standard-of-care arm
  - RR 0.88; 95% CI, 0.60-1.29; P = .51

- In a Doxy-PEP study among cisgender women in Kenya, there was **no impact** of doxycycline postexposure prophylaxis on incident STIs

More To Come

- **Syphilaxis** (Australia) - “An antibiotic every day or two antibiotic pills after sex”
  - Comparing Doxycycline PrEP vs PEP
- **CTN 313: The DaDHS Trial** – “Daily doxycycline or placebo”
  - Comparing Doxycycline PrEP vs placebo
- **DISCO** - Comparing Doxycycline PrEP vs PEP

What We Know About Doxy-PEP

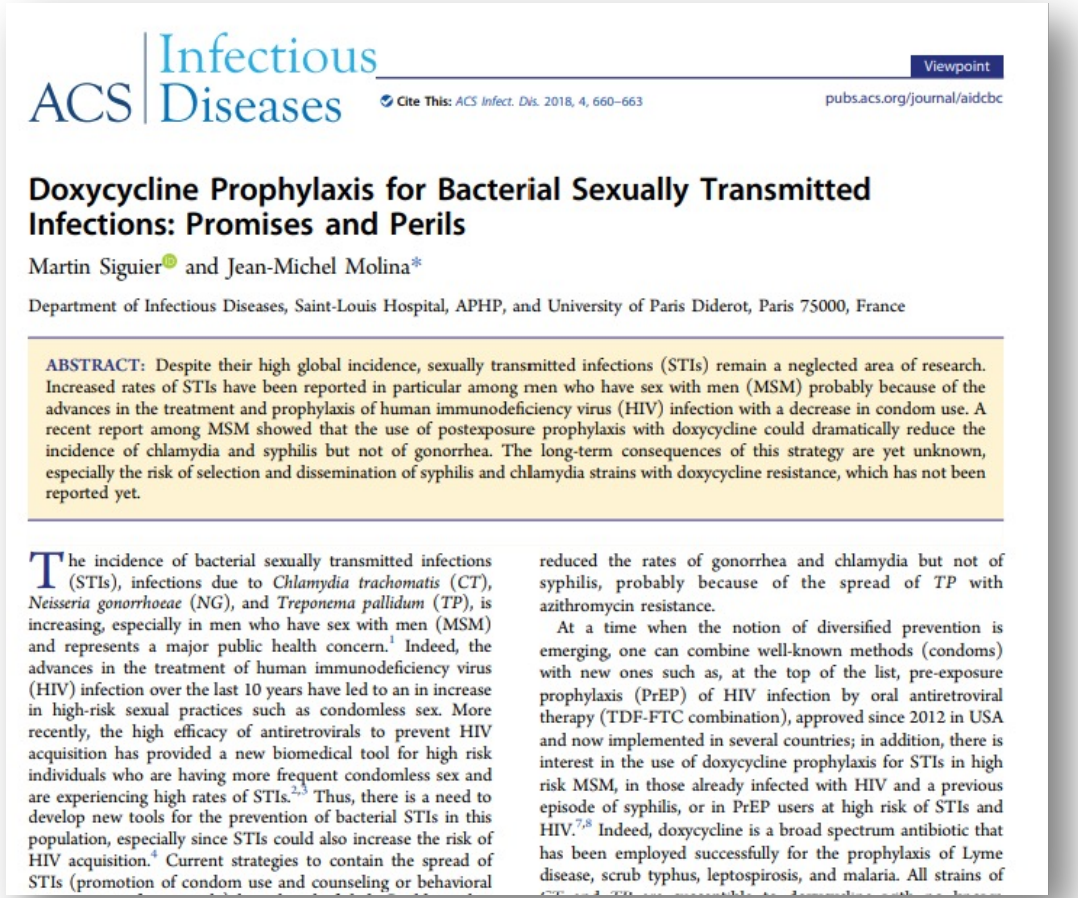
Existing studies on Doxycycline as post-exposure (Doxy-PEP) or pre-exposure (Doxy-PrEP) prophylaxis				
Study		Population	Effectiveness	Pills/month
ANRS IPERGAY	PEP	MSM/TGW taking PrEP	**Reduction** in time to first STI HR 0.53 (0.33-0.85) Reduction seen for CT and syphilis but not GC	6.8
DoxyPEP	PEP	MSM/TGW Taking PrEP or PWH	**Reduction** in STI per quarter RR 0.38 (0.24 – 0.6)	4.O (IQR 1-10)
DoxyVac	PEP	MSM on PrEP	**Reduction** in time to first CT or syphilis HR 0.16 (0.08-0.30). Reduction in time to first GC HR 0.49 (0.32-0.76)	7.0 (IQR 4-11)
dPEP	PEP	Women	**No reduction** in STI incidence RR 0.88 (0.60-1.29)	Not reported

MSM = men who have sex with men, TGW = transgender women, PWH = Persons with HIV, CT = Chlamydia, GC = Gonorrhea, OR = odds ratio, HR = hazards ratio RR = Relative risk reduction () = Confidence intervals IQR() = Interquartile range

- Doxycycline **post-exposure prophylaxis** (PEP) is safe and well tolerated
- Doxy-PEP **prevents** STIs in MSM and transgender women
- Doxy-PEP **did not** prevent STIs in cis-women in the dPEP study

What Do We Know About The Risks of Doxy-PEP?

Doxy-PEP Concerns



ACS Infectious Diseases

Viewpoint

Cite This: *ACS Infect. Dis.* 2018, 4, 660−663

pubs.acs.org/journal/aidcbc

Doxycycline Prophylaxis for Bacterial Sexually Transmitted Infections: Promises and Perils

Martin Siguier and Jean-Michel Molina*

Department of Infectious Diseases, Saint-Louis Hospital, APHP, and University of Paris Diderot, Paris 75000, France

ABSTRACT: Despite their high global incidence, sexually transmitted infections (STIs) remain a neglected area of research. Increased rates of STIs have been reported in particular among men who have sex with men (MSM) probably because of the advances in the treatment and prophylaxis of human immunodeficiency virus (HIV) infection with a decrease in condom use. A recent report among MSM showed that the use of postexposure prophylaxis with doxycycline could dramatically reduce the incidence of chlamydia and syphilis but not of gonorrhea. The long-term consequences of this strategy are yet unknown, especially the risk of selection and dissemination of syphilis and chlamydia strains with doxycycline resistance, which has not been reported yet.

The incidence of bacterial sexually transmitted infections (STIs), infections due to *Chlamydia trachomatis* (*CT*), *Neisseria gonorrhoeae* (*NG*), and *Treponema pallidum* (*TP*), is increasing, especially in men who have sex with men (MSM) and represents a major public health concern.[1] Indeed, the advances in the treatment of human immunodeficiency virus (HIV) infection over the last 10 years have led to an in increase in high-risk sexual practices such as condomless sex. More recently, the high efficacy of antiretrovirals to prevent HIV acquisition has provided a new biomedical tool for high risk individuals who are having more frequent condomless sex and are experiencing high rates of STIs.[2,3] Thus, there is a need to develop new tools for the prevention of bacterial STIs in this population, especially since STIs could also increase the risk of HIV acquisition.[4] Current strategies to contain the spread of STIs (promotion of condom use and counseling or behavioral

reduced the rates of gonorrhea and chlamydia but not of syphilis, probably because of the spread of *TP* with azithromycin resistance.

At a time when the notion of diversified prevention is emerging, one can combine well-known methods (condoms) with new ones such as, at the top of the list, pre-exposure prophylaxis (PrEP) of HIV infection by oral antiretroviral therapy (TDF-FTC combination), approved since 2012 in USA and now implemented in several countries; in addition, there is interest in the use of doxycycline prophylaxis for STIs in high risk MSM, in those already infected with HIV and a previous episode of syphilis, or in PrEP users at high risk of STIs and HIV.[7,8] Indeed, doxycycline is a broad spectrum antibiotic that has been employed successfully for the prophylaxis of Lyme disease, scrub typhus, leptospirosis, and malaria. All strains of

- However, even if these results are encouraging, they should be taken with great caution:

1. Previous trials of antibiotic prophylaxis have shown only limited and transient benefits
2. Risk compensation…might offset early benefits
3. Antibiotic prophylaxis might change the presentation of STIs
4. Impact of doxycycline use on the microbiome remains to be assessed
    - Might select for antibiotic resistance outside the field of STIs
    - The greatest fear is by far the risk of selection of doxycycline resistance to chlamydia and syphilis

- Siguier M, Molina JM. Doxycycline Prophylaxis for Bacterial Sexually Transmitted Infections: Promises and Perils. ACS Infect Dis. 2018;4(5):660-663. doi:10.1021/acsinfecdis.8b00043

Clinical Questions

- How will Doxy-PEP impact sexual behavior?

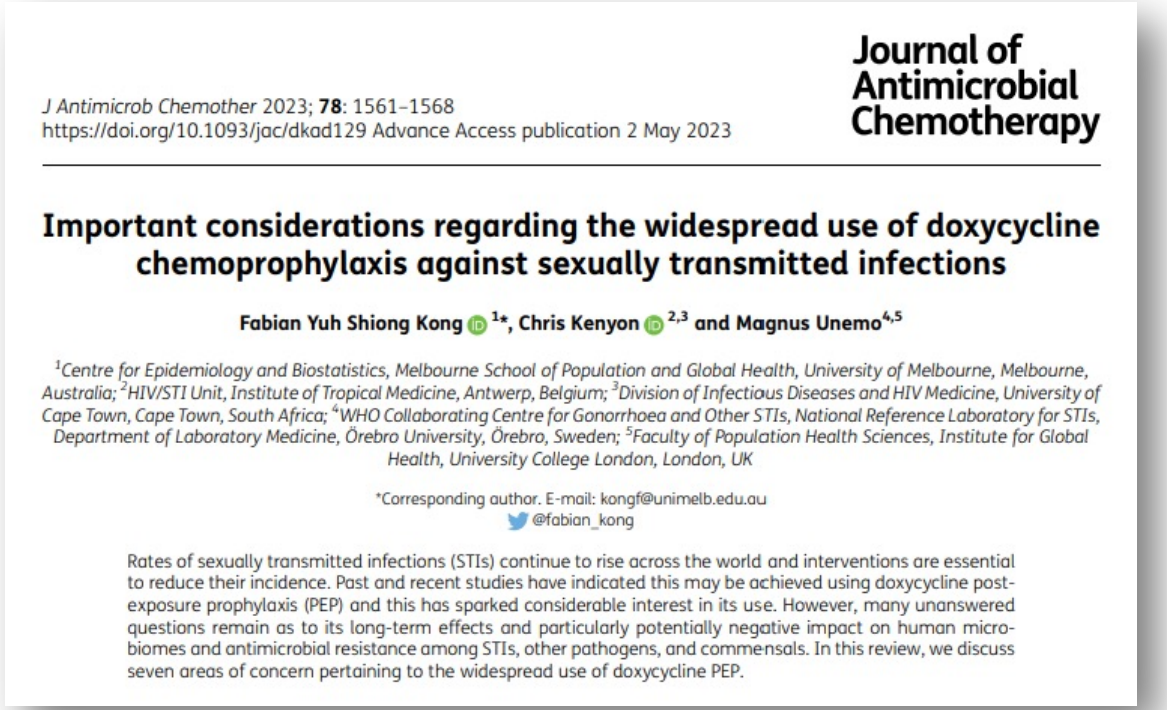
- DoxyPEP and DoxyVAC
  - No impact on sexual behavior
  - Changes in sexual behavior could impact Doxy-PEPs effectiveness

Clinical Questions

- Antibiotic prophylaxis may change the presentation or diagnosis of STIs

- No data so far
- Notable concern about the impact on syphilis serological testing
  - Partial treatment
  - Delayed diagnosis
  - False negatives

Antimicrobial Resistance Concerns



J Antimicrob Chemother 2023; **78**: 1561–1568
https://doi.org/10.1093/jac/dkad129 Advance Access publication 2 May 2023

Journal of Antimicrobial Chemotherapy

Important considerations regarding the widespread use of doxycycline chemoprophylaxis against sexually transmitted infections

Fabian Yuh Shiong Kong [1]*, Chris Kenyon [2,3] and Magnus Unemo [4,5]

[1]*Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Australia;* [2]*HIV/STI Unit, Institute of Tropical Medicine, Antwerp, Belgium;* [3]*Division of Infectious Diseases and HIV Medicine, University of Cape Town, Cape Town, South Africa;* [4]*WHO Collaborating Centre for Gonorrhoea and Other STIs, National Reference Laboratory for STIs, Department of Laboratory Medicine, Örebro University, Örebro, Sweden;* [5]*Faculty of Population Health Sciences, Institute for Global Health, University College London, London, UK*

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@fabian_kong

Rates of sexually transmitted infections (STIs) continue to rise across the world and interventions are essential to reduce their incidence. Past and recent studies have indicated this may be achieved using doxycycline post-exposure prophylaxis (PEP) and this has sparked considerable interest in its use. However, many unanswered questions remain as to its long-term effects and particularly potentially negative impact on human microbiomes and antimicrobial resistance among STIs, other pathogens, and commensals. In this review, we discuss seven areas of concern pertaining to the widespread use of doxycycline PEP.

1. Antimicrobial Resistance in STIs
    1. *Treponema pallidum*
    2. *Chlamydia trachomatis*
    3. *Mycoplasma Genitalium*
    4. *Neisseria Gonorrhea*
2. Antimicrobial Resistance in other bacterial species
    1. Commensal bacteria

- Kong FYS, Kenyon C, Unemo M. Important considerations regarding the widespread use of doxycycline chemoprophylaxis against sexually transmitted infections. J Antimicrob Chemother. 2023;78(7):1561-1568. doi:10.1093/jac/dkad129

Limited Antibiotics in the Pipeline

The Journal of Antibiotics (2023) 76:431–473
https://doi.org/10.1038/s41429-023-00629-8

Japan Antibiotics Research Association

The Society for Actinomycetes Japan

REVIEW ARTICLE

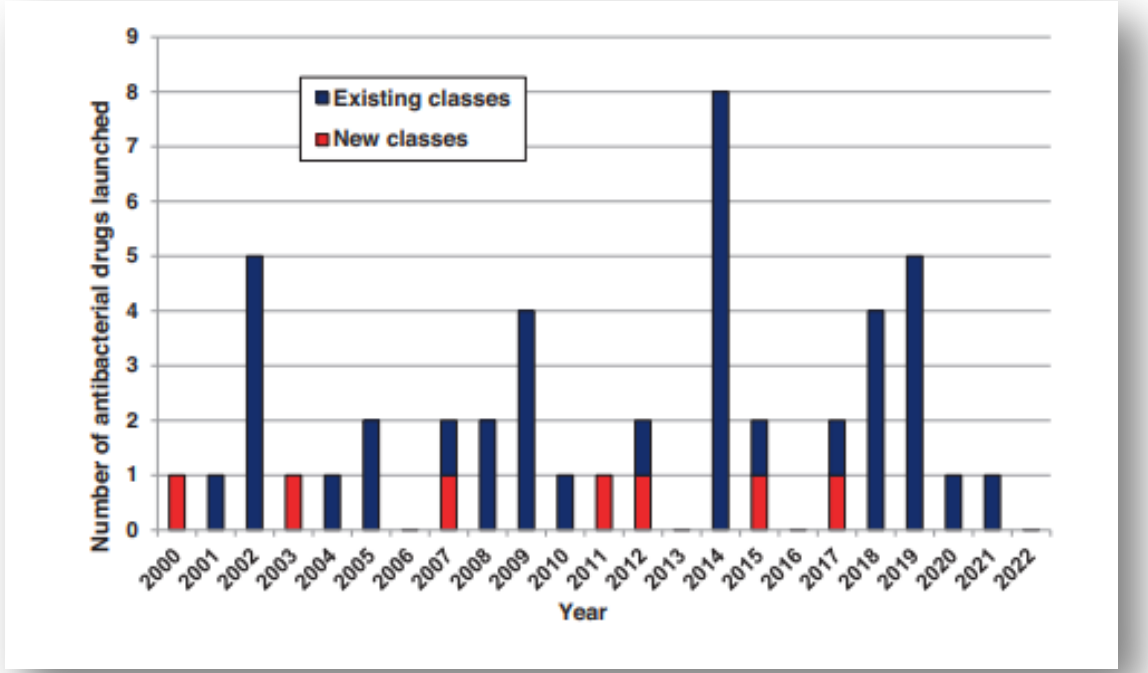
Antibiotics in the clinical pipeline as of December 2022

Mark S. Butler[1] · Ian R. Henderson[1] · Robert J. Capon[1] · Mark A. T. Blaskovich[1]

Received: 2 March 2023 / Revised: 20 April 2023 / Accepted: 25 April 2023 / Published online: 8 June 2023

Abstract

The need for new antibacterial drugs to treat the increasing global prevalence of drug-resistant bacterial infections has clearly attracted global attention, with a range of existing and upcoming funding, policy, and legislative initiatives designed to revive antibacterial R&D. It is essential to assess whether these programs are having any real-world impact and this review continues our systematic analyses that began in 2011. Direct-acting antibacterials (47), non-traditional small molecule antibacterials (5), and β-lactam/β-lactamase inhibitor combinations (10) under clinical development as of December 2022 are described, as are the three antibacterial drugs launched since 2020. Encouragingly, the increased number of early-stage clinical candidates observed in the 2019 review increased in 2022, although the number of first-time drug approvals from 2020 to 2022 was disappointingly low. It will be critical to monitor how many Phase-I and -II candidates move into Phase-III and beyond in the next few years. There was also an enhanced presence of novel antibacterial pharmacophores in early-stage trials, and at least 18 of the 26 phase-I candidates were targeted to treat Gram-negative bacteria infections. Despite the promising early-stage antibacterial pipeline, it is essential to maintain funding for antibacterial R&D and to ensure that plans to address late-stage pipeline issues succeed.



• Butler MS, Henderson IR, Capon RJ, Blaskovich MAT. Antibiotics in the clinical pipeline as of December 2022. J Antibiot (Tokyo). 2023;76(8):431-473. doi:10.1038/s41429-023-00629-8

Including for STIs

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Table 3 Antibiotics with NDA/MAA submitted or in phase-III clinical trials (structures in Figs. 3 and 4)

Name (synonym)[a]	Compound class (lead source)	Mode of action[a]	Administration; indication (developer)
NDA/MAA			
solithromycin (**6**) (T-4288)	erythromycin (NP)	protein synthesis inhibition	IV/po; respiratory tract infection (FUJIFILM Toyama)
Phase-III			
sulopenem (**6**) (IV) sulopenem etzadroxil (**7**) (prodrug) + probenecid (**8**)	penem (NP)	PBP (cell wall)	po; uUTI, cUTI and cIAI (Iterum Therapeutics)
nafithromycin (**9**) (WCK 4873)	macrolide (NP)	protein synthesis	po; CABP (Wockhardt)
gepotidacin (**10**) (GSK-2140944)	triazaacenaphthylene (S)	DNA gyrase (GyrA) — different to quinolones	po; UTI and gonorrhea (GSK)
zoliflodacin (**11**) (ETX0914)	spiropyrimidinetrione (S)	DNA gyrase (GyrB)	po; gonorrhea (Innoviva / GARDP)
Phase-II/III			
benapenem (**12**)	carbapenem (NP)	PBP (cell wall)	IV; UTI (Sihuan Pharmaceuticals)
epetraborole (**13**) (BRII-658)	oxaborole (S)	leucyl-tRNA synthetase (LeuRS) – protein synthesis	po; NTM with a focus on *M. avium* (AN2 Therapeutics / Brii Biosciences)

CABP community-acquired bacterial pneumonia, *cIAI* complicated intra-abdominal infections, *cUTI* complicated urinary tract infections, *IV* intravenous, *NP* natural product, *PBP* penicillin binding protein, *po per orem* (oral), *NTM* non-tuberculosis mycobacteria, *S* synthetic, *uUTI* uncomplicated urinary tract infections, *UTI* urinary tract infections

[a]Compounds with new pharmacophores and MoA are underlined

- Butler MS, Henderson IR, Capon RJ, Blaskovich MAT. Antibiotics in the clinical pipeline as of December 2022. J Antibiot (Tokyo). 2023;76(8):431-473. doi:10.1038/s41429-023-00629-8

Antimicrobial Resistance

Chlamydia

- No clinical resistance to tetracyclines in *Chlamydia trachomatis*
- Tetracycline resistance has been seen in C.suis (pigs)
  - tetC (efflux pump)

Syphilis

- No clinical resistance to tetracyclines in *Treponema pallidum*
- Widespread macrolide resistance was seen with a single-point mutation

Benamri I, Azzouzi M, Sanak K, Moussa A, Radouani F. An overview of genes and mutations associated with Chlamydiae species' resistance to antibiotics. Ann Clin Microbiol Antimicrob. 2021;20(1):59. Published 2021 Sep 3. doi:10.1186/s12941-021-00465-4

Beale MA, Marks M, Sahi SK, et al. Genomic epidemiology of syphilis reveals independent emergence of macrolide resistance across multiple circulating lineages. Nat Commun. 2019;10(1):3255. Published 2019 Jul 22. doi:10.1038/s41467-019-11216-7

Antimicrobial Resistance – M. Genitalium

- Intrinsically resistant to:
  - Cell wall and folic acid inhibitors
- High resistance rates to:
  - Protein synthesis inhibitors
    - Macrolides 77%
    - Tetracyclines, 60%
  - Nucleic acid synthesis inhibitors
    - quinolones, 90%

Antimicrobial Resistance – M. Genitalium

Clinical Infectious Diseases

MAJOR ARTICLE

Outcomes of Resistance-guided Sequential Treatment of *Mycoplasma genitalium* Infections: A Prospective Evaluation

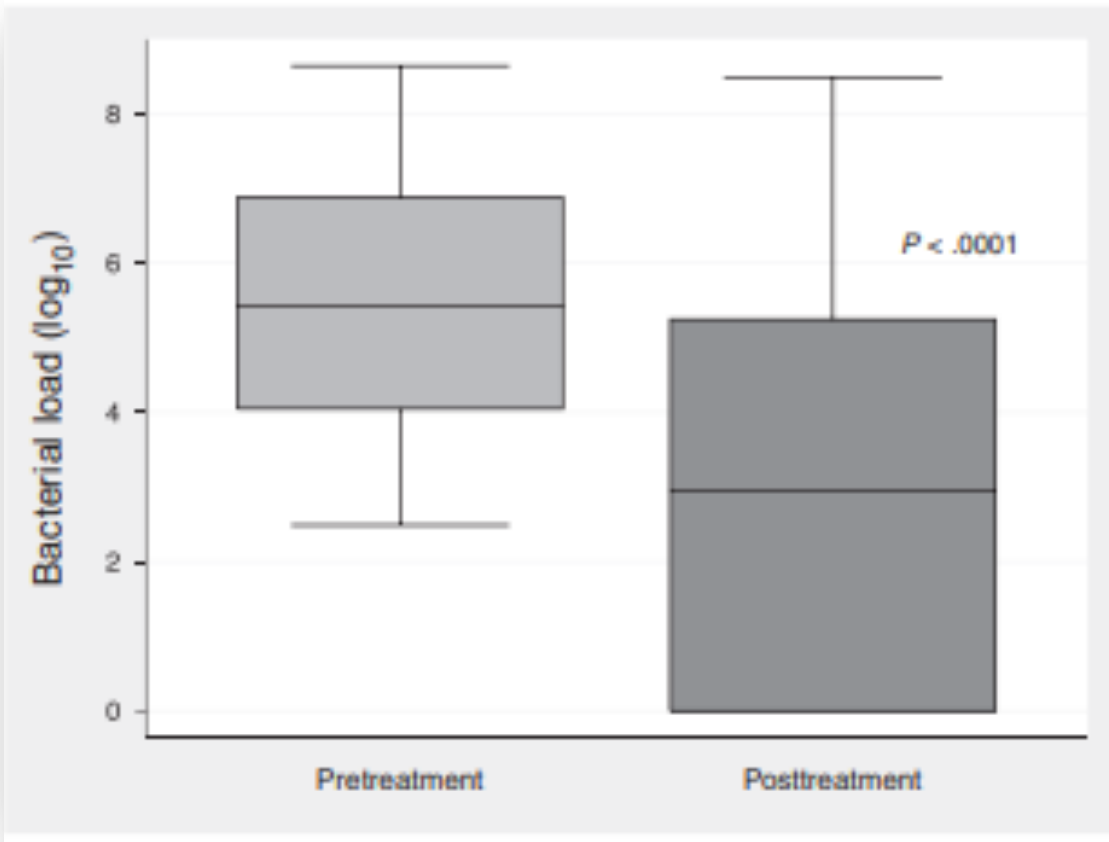
Tim R. H. Read,[1,2] Christopher K. Fairley,[1,2] Gerald L. Murray,[3,4,5,6] Jorgen S. Jensen,[7] Jennifer Danielewski,[3,4] Karen Worthington,[2] Michelle Doyle,[2] Elisa Mokany,[8] Litty Tan,[8] Eric P. F. Chow,[1,2] Suzanne M. Garland,[3,4,6,9] and Catriona S. Bradshaw[1,2]

[1]Central Clinical School, Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, [2]Melbourne Sexual Health Centre, Alfred Health, Carlton, [3]Murdoch Children's Research Institute, Parkville, [4]Department of Microbiology and Infectious Diseases, Royal Women's Hospital, Melbourne, [5]Infection and Immunity Program, Monash Biomedicine Discovery Institute, and [6]Royal Children's Hospital, Melbourne, Victoria, Australia; [7]Statens Serum Institut, Copenhagen, Denmark; [8]SpeeDx Pty Ltd, Eveleigh, New South Wales, and [9]Department of Obstetrics and Gynaecology, University of Melbourne, Victoria, Australia

(See the Major Article by Braun et al on pages 569-76 and Editorial commentary by Sulkowski on pages 577-9.)

Background. Rising macrolide and quinolone resistance in *Mycoplasma genitalium* necessitate new treatment approaches. We evaluated outcomes of sequential antimicrobial therapy for *M. genitalium* guided by a macrolide-resistance assay.

Methods. In mid-2016, Melbourne Sexual Health Centre switched from azithromycin to doxycycline (100 mg twice daily for 7 days) for nongonococcal urethritis, cervicitis, and proctitis. Cases were tested for *M. genitalium* and macrolide-resistance mutations (MRMs) by polymerase chain reaction. Directly after doxycycline, MRM-negative infections received 2.5 g azithromycin (1 g, then 500 mg daily for 3 days), and MRM-positive infections received sitafloxacin (100 mg twice daily for 7 days). Assessment of test of cure and reinfection risk occurred 14–90 days after the second antibiotic.



- Read TRH, Fairley CK, Murray GL, et al. Outcomes of Resistance-guided Sequential Treatment of Mycoplasma genitalium Infections: A Prospective Evaluation. Clin Infect Dis. 2019;68(4):554-560. doi:10.1093/cid/ciy477

Antimicrobial Resistance - Gonorrhea

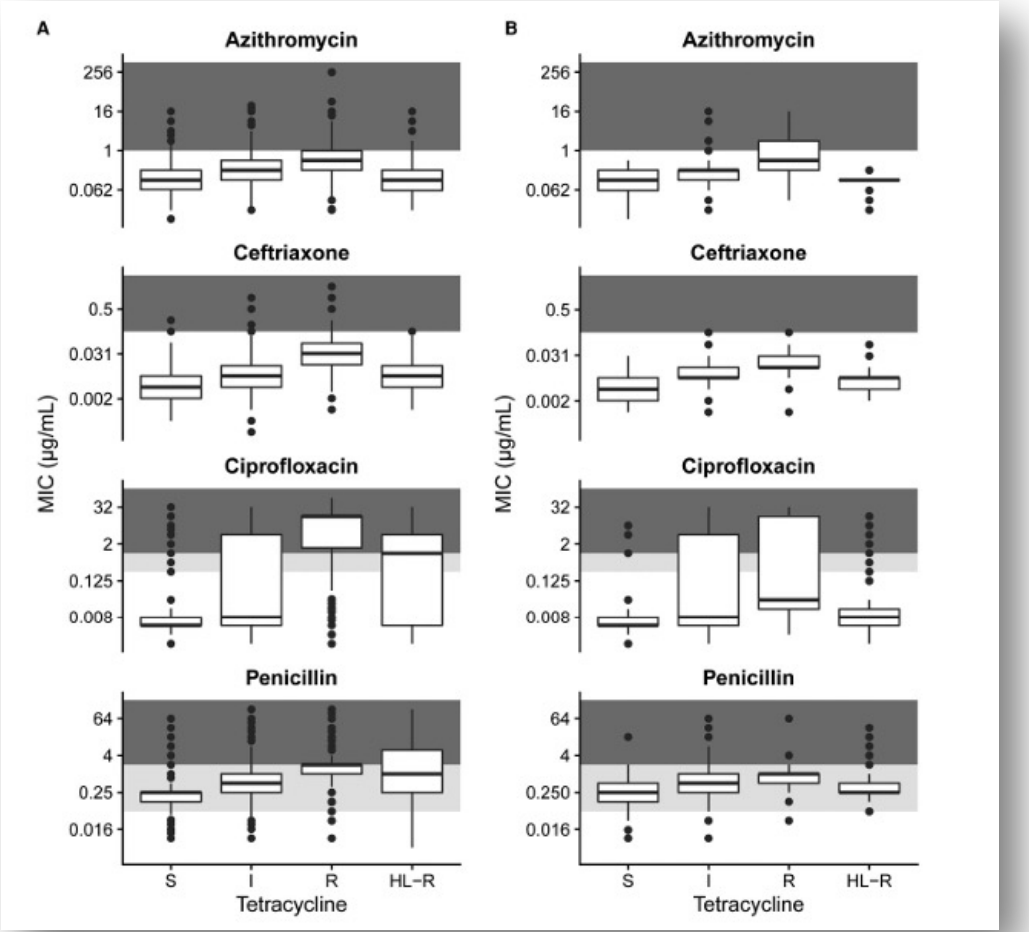
Clinical Infectious Diseases

BRIEF REPORT

A Genomic Perspective on the Near-term Impact of Doxycycline Post-exposure Prophylaxis on *Neisseria gonorrhoeae* Antimicrobial Resistance

Tatum D. Mortimer and Yonatan H. Grad

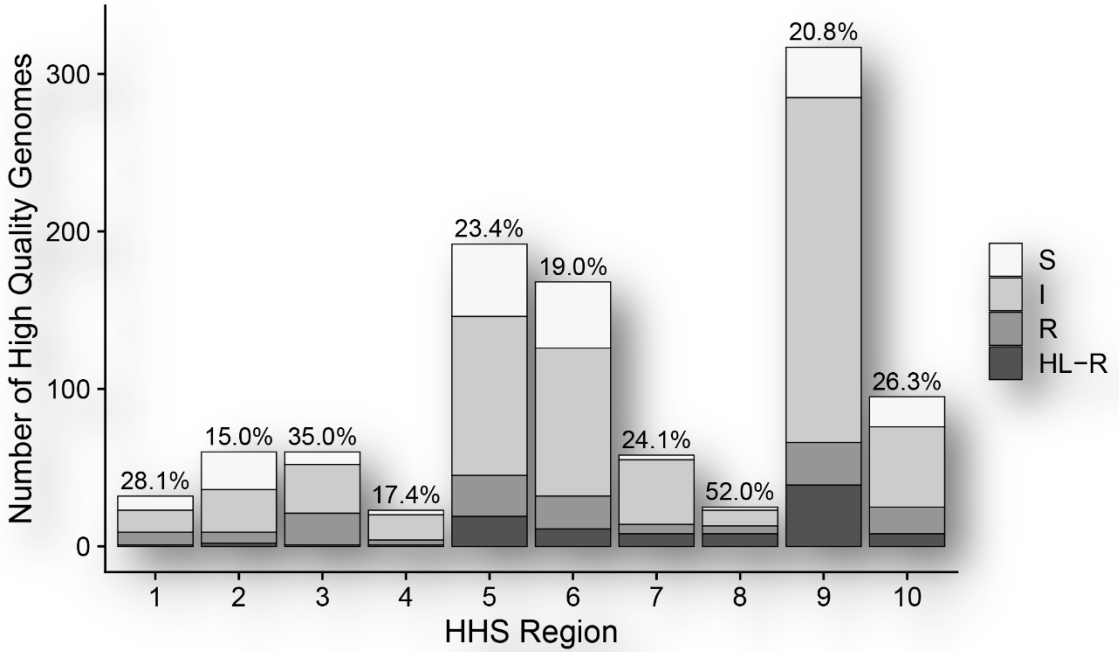
Department of Immunology and Infectious Diseases, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA



- Mortimer TD, Grad YH. A genomic perspective on the near-term impact of doxycycline post-exposure prophylaxis on Neisseria gonorrhoeae antimicrobial resistance [published online ahead of print, 2023 May 4]. Clin Infect Dis. 2023;ciad279. doi:10.1093/cid/ciad279

Antimicrobial Resistance - Gonorrhea

Tetracycline Susceptibility By HHS Region

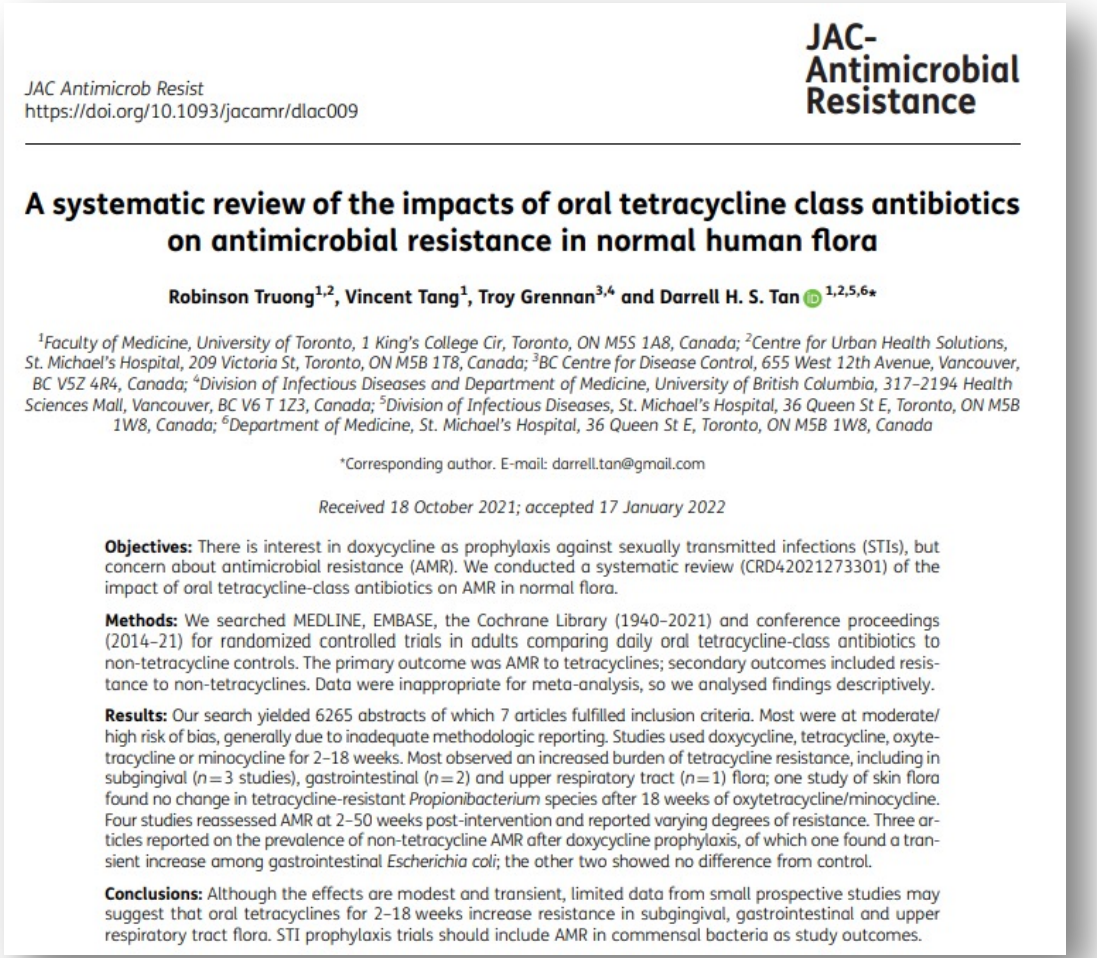


Tetracycline Susceptibility By Sexual Preferences

	S	I	R	HL-R
MSM	10.3%	62.9%	15.9%	10.9%
MSW	23.0%	55.7%	12.8%	8.5%
MSMW	13.2%	60.3%	14.7%	11.8%

- Mortimer TD, Grad YH. A genomic perspective on the near-term impact of doxycycline post-exposure prophylaxis on Neisseria gonorrhoeae antimicrobial resistance [published online ahead of print, 2023 May 4]. Clin Infect Dis. 2023;ciad279. doi:10.1093/cid/ciad279

Antimicrobial Resistance - Commensals



JAC Antimicrob Resist
https://doi.org/10.1093/jacamr/dlac009

JAC-Antimicrobial Resistance

A systematic review of the impacts of oral tetracycline class antibiotics on antimicrobial resistance in normal human flora

Robinson Truong[1,2], Vincent Tang[1], Troy Grennan[3,4] and Darrell H. S. Tan[1,2,5,6]*

[1]Faculty of Medicine, University of Toronto, 1 King's College Cir, Toronto, ON M5S 1A8, Canada; [2]Centre for Urban Health Solutions, St. Michael's Hospital, 209 Victoria St, Toronto, ON M5B 1T8, Canada; [3]BC Centre for Disease Control, 655 West 12th Avenue, Vancouver, BC V5Z 4R4, Canada; [4]Division of Infectious Diseases and Department of Medicine, University of British Columbia, 317–2194 Health Sciences Mall, Vancouver, BC V6 T 1Z3, Canada; [5]Division of Infectious Diseases, St. Michael's Hospital, 36 Queen St E, Toronto, ON M5B 1W8, Canada; [6]Department of Medicine, St. Michael's Hospital, 36 Queen St E, Toronto, ON M5B 1W8, Canada

*Corresponding author. E-mail: darrell.tan@gmail.com

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Objectives: There is interest in doxycycline as prophylaxis against sexually transmitted infections (STIs), but concern about antimicrobial resistance (AMR). We conducted a systematic review (CRD42021273301) of the impact of oral tetracycline-class antibiotics on AMR in normal flora.

Methods: We searched MEDLINE, EMBASE, the Cochrane Library (1940–2021) and conference proceedings (2014–21) for randomized controlled trials in adults comparing daily oral tetracycline-class antibiotics to non-tetracycline controls. The primary outcome was AMR to tetracyclines; secondary outcomes included resistance to non-tetracyclines. Data were inappropriate for meta-analysis, so we analysed findings descriptively.

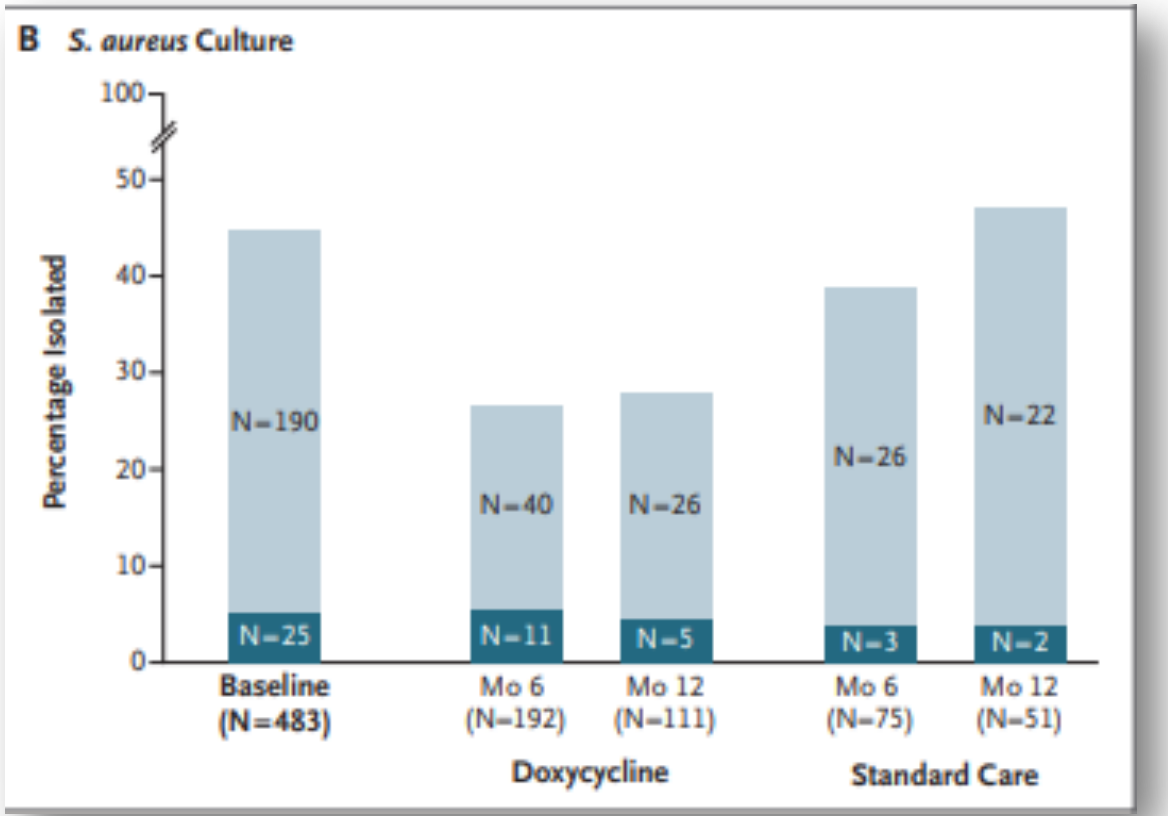
Results: Our search yielded 6265 abstracts of which 7 articles fulfilled inclusion criteria. Most were at moderate/high risk of bias, generally due to inadequate methodologic reporting. Studies used doxycycline, tetracycline, oxytetracycline or minocycline for 2–18 weeks. Most observed an increased burden of tetracycline resistance, including in subgingival ($n=3$ studies), gastrointestinal ($n=2$) and upper respiratory tract ($n=1$) flora; one study of skin flora found no change in tetracycline-resistant *Propionibacterium* species after 18 weeks of oxytetracycline/minocycline. Four studies reassessed AMR at 2–50 weeks post-intervention and reported varying degrees of resistance. Three articles reported on the prevalence of non-tetracycline AMR after doxycycline prophylaxis, of which one found a transient increase among gastrointestinal *Escherichia coli*; the other two showed no difference from control.

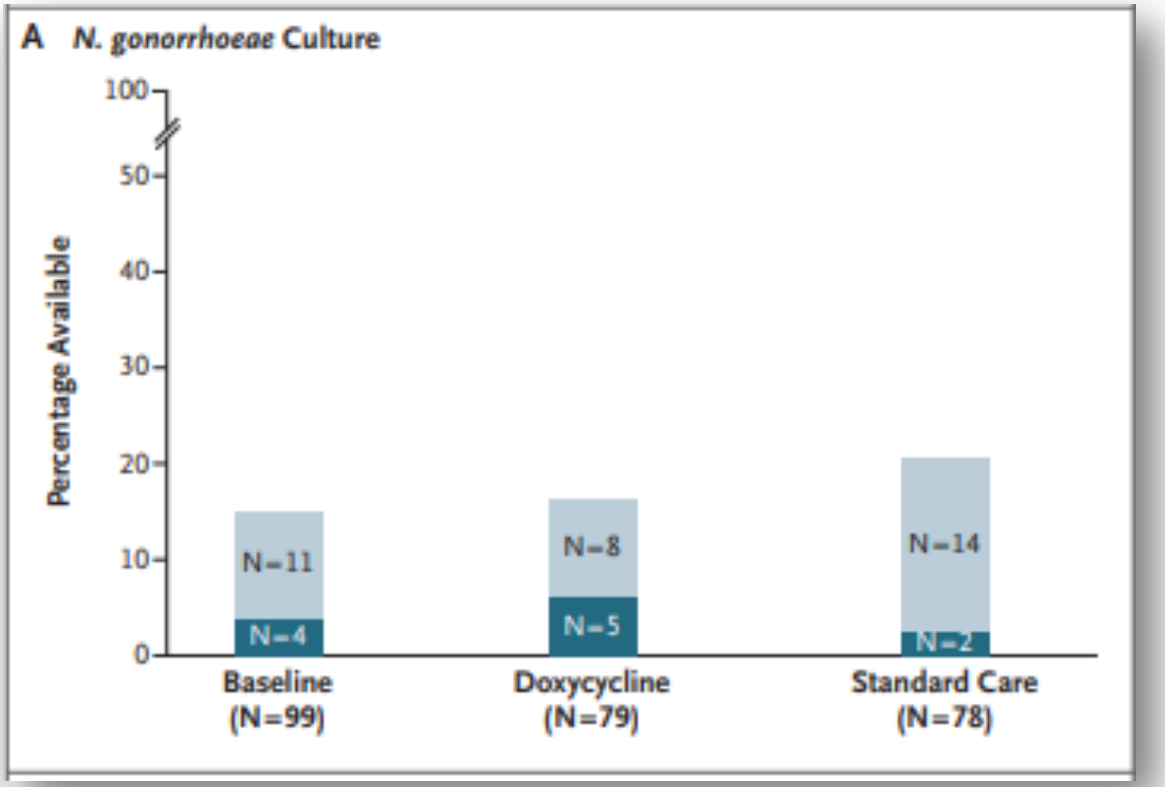
Conclusions: Although the effects are modest and transient, limited data from small prospective studies may suggest that oral tetracyclines for 2–18 weeks increase resistance in subgingival, gastrointestinal and upper respiratory tract flora. STI prophylaxis trials should include AMR in commensal bacteria as study outcomes.

- Limited data from small prospective studies may suggest that oral tetracyclines for 2–18 weeks increase resistance in subgingival, gastrointestinal and upper respiratory tract flora.

- Truong R, Tang V, Grennan T, Tan DHS. A systematic review of the impacts of oral tetracycline class antibiotics on antimicrobial resistance in normal human flora. JAC Antimicrob Resist. 2022;4(1):dlac009. Published 2022 Feb 15. doi:10.1093/jacamr/dlac009

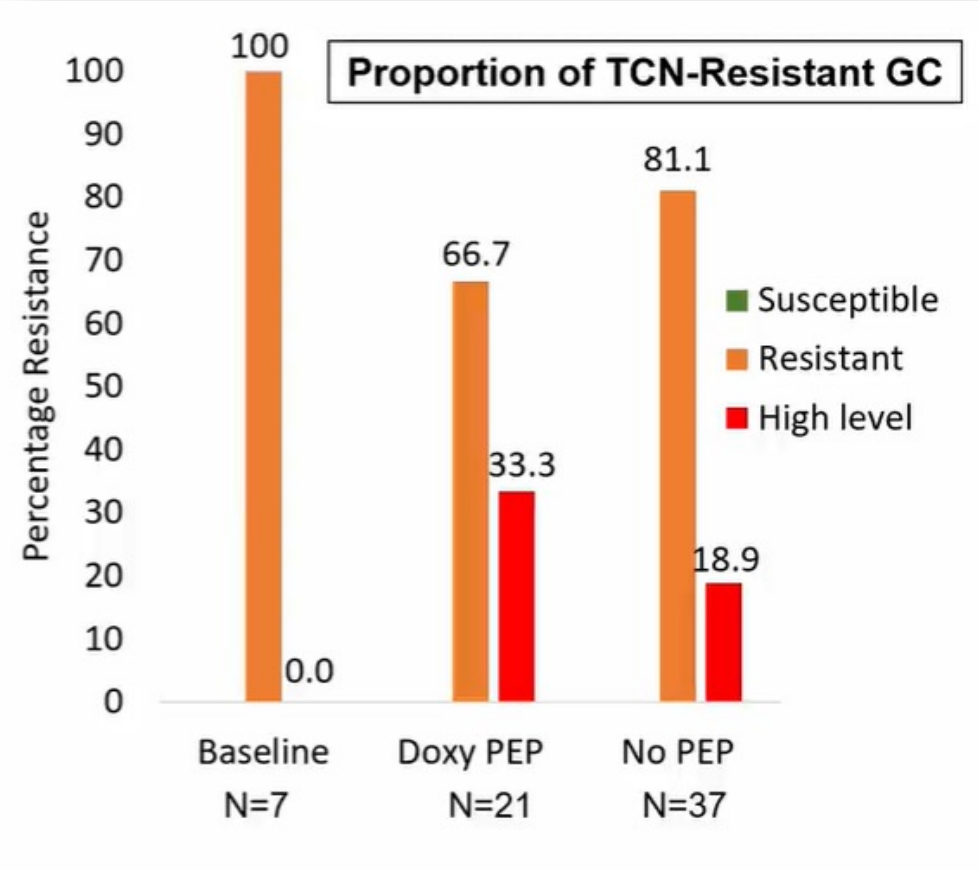
Antimicrobial Resistance – DoxyPEP Study

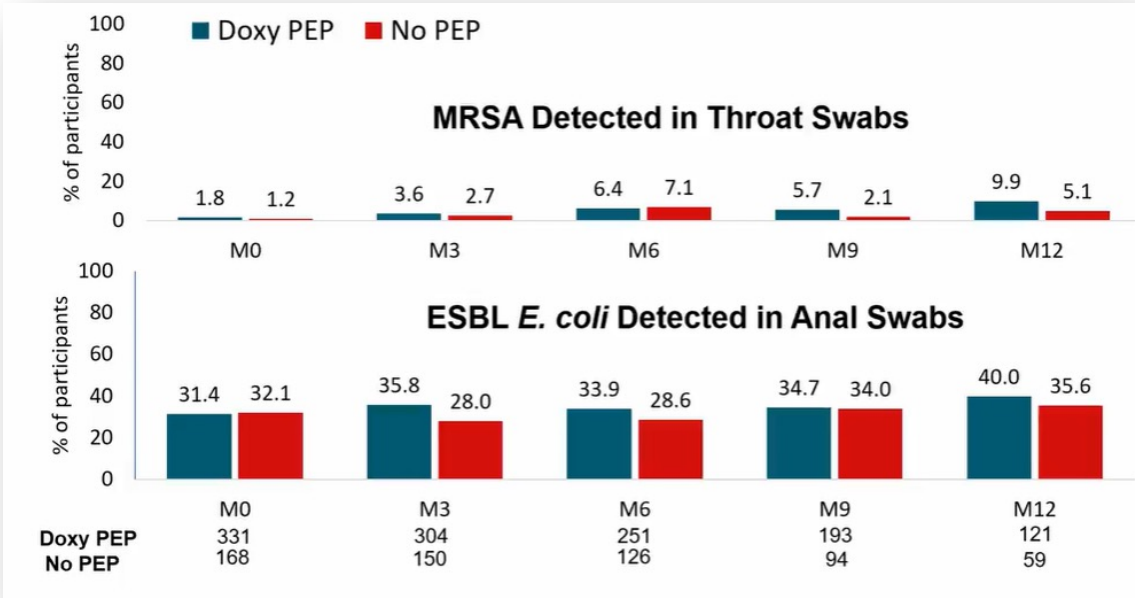




- Luetkemeyer AF, Donnell D, Dombrowski JC, et al. Postexposure Doxycycline to Prevent Bacterial Sexually Transmitted Infections. N Engl J Med. 2023;388(14):1296-1306. doi:10.1056/NEJMoa2211934

Antimicrobial Resistance – DoxyVac Study





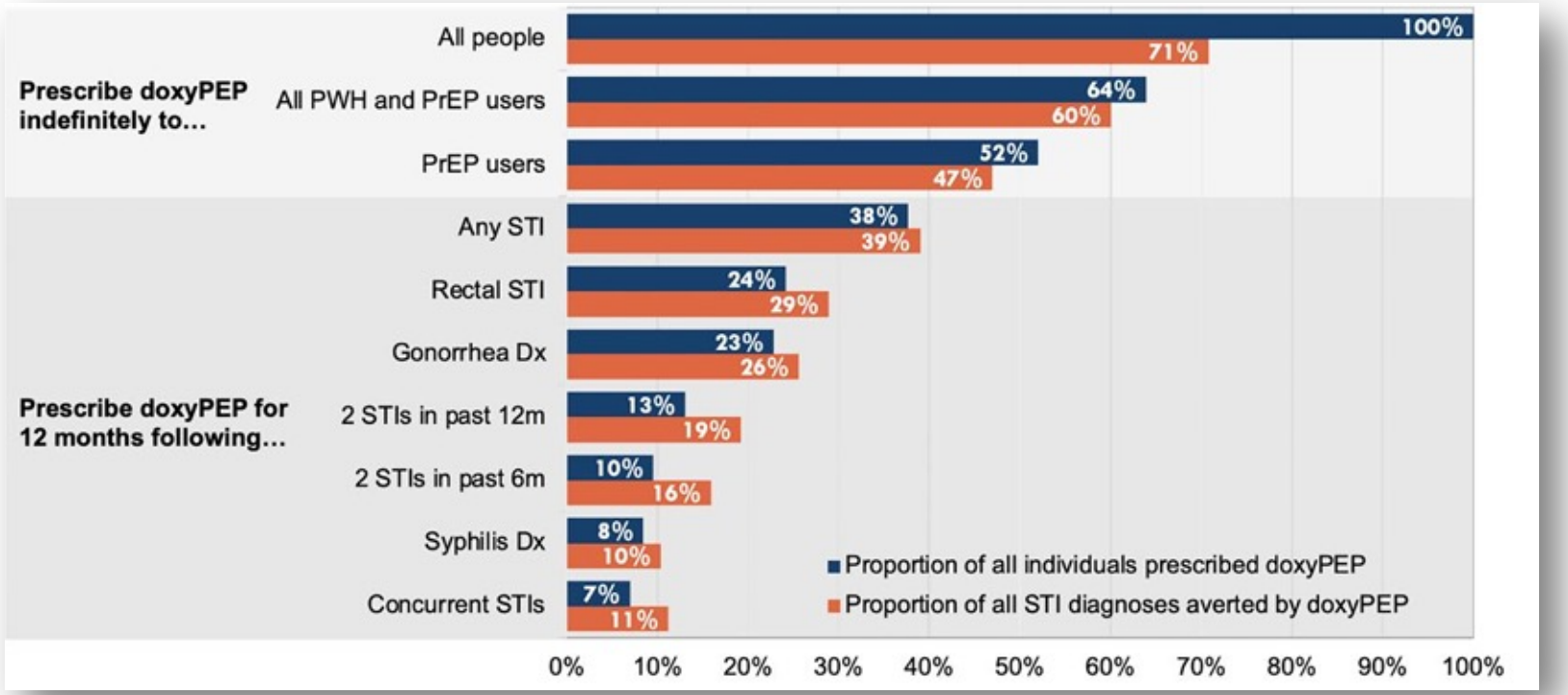
COLUMBIA | COLUMBIA UNIVERSITY IRVING MEDICAL CENTER

- Molina et al DOXYVAC CROI 2023 Abstract 119
- Liu AY, Buchbinder SP. CROI 2023: Epidemiologic Trends and Prevention for HIV and Other Sexually Transmitted Infections. Top Antivir Med. 2023;31(3):468-492.

NEW YORK CITY STD HIV PREVENTION TRAINING CENTER

Implementation Questions

- **Who should be given Doxy-PEP?**
- What is the proper interval for STI testing for individuals on Doxy-PEP?



- Traeger MW, Mayer KH, Krakower DS, Gitin S, Jenness SM, Marcus JL. Potential impact of doxycycline post-exposure prophylaxis prescribing strategies on incidence of bacterial sexually transmitted infections [published online ahead of print, 2023 Aug 18]. Clin Infect Dis. 2023;ciad488. doi:10.1093/cid/ciad488

Implementation Questions

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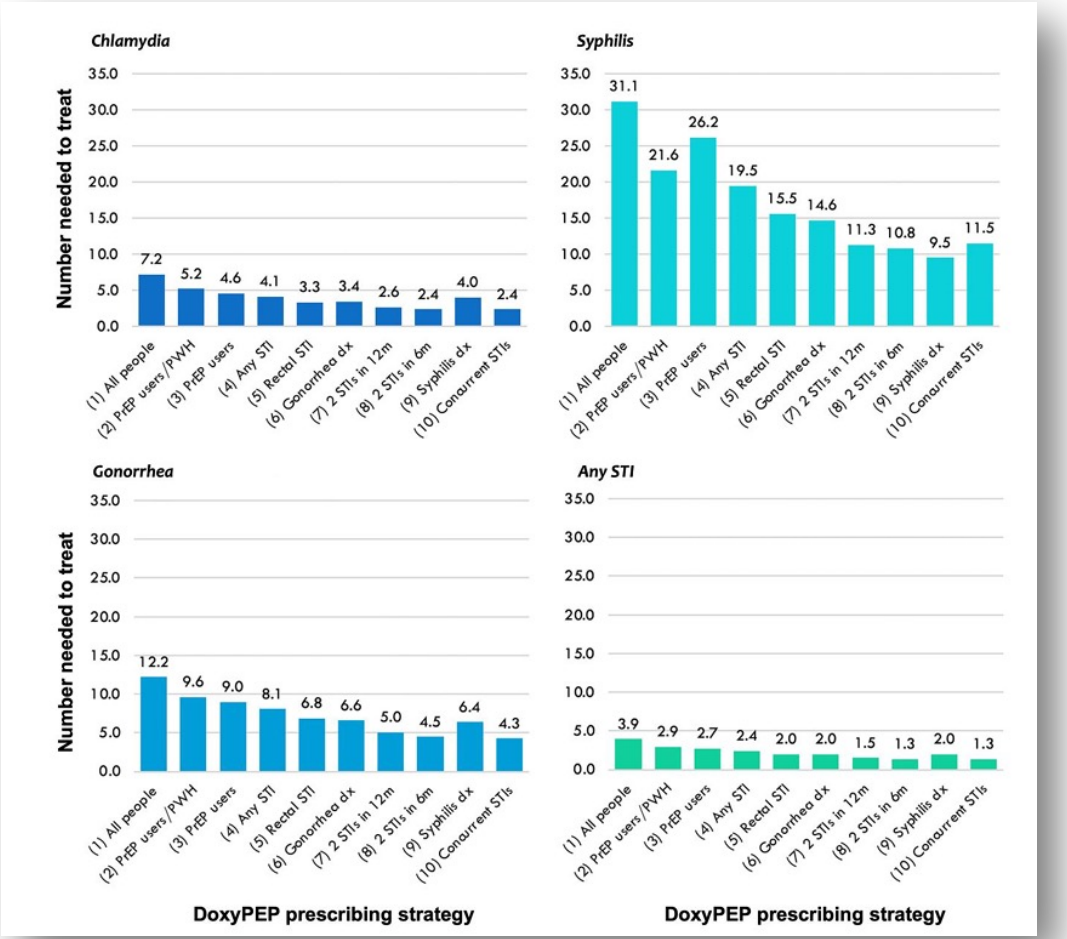

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Doxy-PEP **Will** Increase Doxycycline Usage

Correspondence

Estimating changes in antibiotic consumption in the USA with the introduction of doxycycline post-exposure prophylaxis

Doxycycline as a post-exposure prophylaxis (doxy-PEP) reduced the risk of bacterial sexually transmitted infections (STIs) in a randomised controlled trial of men who have sex with men taking HIV pre-exposure prophylaxis (PrEP), transgender women taking HIV PrEP, and people living with HIV.[1] There is concern that increased consumption of doxycycline might increase antimicrobial resistance, including doxycycline-resistant *Neisseria gonorrhoeae*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*.[2-4]

Antibiotic use might change with the introduction of doxy-PEP; estimating this change could inform considerations of the risks of antimicrobial resistance and the benefits of STI prevention. We estimated the first-order expected increase in antibiotic consumption in the USA under several doxy-PEP prescribing scenarios (appendix pp 1–2). We accounted for defined STI in the past year.[1] If 75% of people in this population began to take doxy-PEP, monthly antibiotic consumption would increase by approximately 2·52 million doses (ie, doxy-PEP consumption of 2·58 million doses minus 62 100 antibiotic doses that would otherwise have been used for bacterial STI treatment; appendix p 6). If the entire eligible population began to take doxy-PEP, monthly antibiotic consumption would be expected to increase by 3·36 million doses (appendix p 7).

A retrospective analysis of ten prescribing strategies based on the PrEP use, HIV status, and bacterial STI history of people predicted substantial variation across the strategies in the number of infections averted per person taking doxy-PEP.[5] The prescribing strategy with the lowest number needed to treat to prevent a chlamydia infection was a diagnosis of two bacterial STIs within a 6-month period. 75% implementation of this strategy among men who have sex with men taking HIV PrEP and people living with HIV would lead to an increase in monthly antibiotic consumption of 0·28 million doses in the USA, whereas widespread (ie, 100%) implementation would lead to an increase of 0·37 million doses (appendix p 7). Among bacterial STI history-based prescribing strategies, year while maintaining similar levels of monthly doxy-PEP consumption and reductions in chlamydia infection risk as reported for people taking HIV PrEP (appendix p 3).

These estimates suggest that doxycycline consumption in the USA will increase with the introduction of doxy-PEP, even when accounting for the reduction in antibiotics used to treat chlamydia, gonorrhoea, and syphilis; the extent of this increase will depend on the size of the population taking doxy-PEP. Monitoring changes in antibiotic consumption, disease incidence, and burden of resistance will be important to understand the effects of doxy-PEP.

This work was supported by the US National Institute of Allergy and Infectious Diseases (grant numbers R01 AI132606 and R01 AI153521) and the US Centers for Disease Control and Prevention (contract number 200–2016–91779), paid to YHG. The findings, conclusions, and views expressed are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. KIOR declares no competing interests.

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See Online for appendix

- "Fully balancing doxy-PEP consumption …would require **restricting prescriptions to a group with an incidence of 7·8 infections per person year**…
- Doxycycline consumption in the USA will increase with the introduction of doxy-PEP, even when accounting for the reduction in antibiotics used
- Monitoring changes in antibiotic consumption, disease incidence, and burden of resistance will be important to understand the effects of doxy-PEP

- https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(23)00314-2/fulltext#articleInformation

Implementation Questions

- Who should be given DoxyPEP?
- **What is the proper interval for STI testing for individuals on Doxy-PEP?**

Population	Recommendations
Men who have sex with men	At least annually, test at each site of exposure (urethra, rectum) for sexually active MSM regardless of condom use or every 3-6 months **if at increased risk**.
Patients taking PrEP	All patients starting and taking oral PrEP should have genitourinary and extra-genital testing performed at baseline and every 3 months.
Persons living with HIV	For sexually active individuals, screen at first HIV evaluation and at least annually thereafter. More frequent screening might be appropriate depending **on individual risk behaviors** and local epidemiology
Non-pregnant Women	Test at least annually for sexually active women under 25 years of age and those aged 25 years and older **if at increased risk** Rectal chlamydial testing can be considered in females **based on sexual behaviors and exposure** through shared clinical decision making.
Men who have sex with women***	Consider screening young men in high prevalence clinical settings (adolescent and STI clinics and correctional facilities)
Pregnant Women	All pregnant women under 25 years of age and those aged 25 years and older **if at increased risk**. retest during 3rd trimester if under 25 years of age or at risk.

• Workowski KA, Bachmann LH, Chan PA, et al. Sexually Transmitted Infections Treatment Guidelines, 2021. MMWR Recomm Rep. 2021;70(4):1-187. Published 2021 Jul 23. doi:10.15585/mmwr.rr7004a1

Current BASHH Recommendations

BASHH column

BASHH updated position statement on doxycycline as prophylaxis for sexually transmitted infections

Manik Kohli [1,2] Nicholas Medland,[3,4] Helen Fifer [5] John Saunders [1,5]

In 2017, BASHH and Public Health England, now the UK Health Security Agency (UKHSA), published a position statement on the use of doxycycline as prophylaxis for STIs.[1] It advised 'extreme caution in the use of doxycycline [as post-exposure prophylaxis (PEP)]…[and] that the use of doxycycline PEP should be restricted to the research setting'. However, increasingly evidence suggests that individuals at higher risk of acquiring bacterial STIs are already using antibiotics to prevent acquisition, accessed through several routes.[2–5] Clinicians are therefore likely to be seeing patients who are self-sourcing antibiotics as STI prophylaxis. For that reason, and to support a person-centred approach to care, the BASHH position statement has been updated. It now includes information about key studies to date and concerns around antimicrobial resistance (AMR) in sexually and non-sexually transmitted infections, as well as providing recommendations for clinicians for how to advise patients about STI prophylaxis. Importantly, it remains the case that doxycycline taken as PEP or pre-exposure prophylaxis (PrEP) for STIs is not endorsed by BASHH or UKHSA. This remains in line with international counterparts.[6] The full position statement is available on the BASHH website: (https://wwwbashhorg/guidelines).

STI prophylaxis is the use of antibiotics as PEP or PrEP to reduce the risk of acquiring certain bacterial STIs. Only the use of doxycycline to prevent syphilis and chlamydia in men who have sex with men (MSM) and transgender women has been researched with a single published study powered to show efficacy.[7] This open-label, randomised controlled trial (RCT) explored the efficacy of doxycycline PEP taken as a single 200 mg dose within the first 24 hours, and no later than 72 hours, after condomless sex among 232 MSM and transgender women using HIV-PrEP. A significant decrease was observed in the occurrence of first episode of chlamydia and for first episode of syphilis. No significant difference in the incidence of gonorrhoea was observed. An earlier open-label, pilot RCT of 100 mg doxycycline daily as PrEP involving 30 MSM living with HIV did observe reductions in both syphilis diagnosis, and diagnosis of either chlamydia or gonorrhoea, that were not statistically significant.[8] Several further studies of doxycycline PrEP and PEP are ongoing.[7 9]

Despite the lack of a large evidence base, up to 10% of HIV-PrEP-using MSM report taking antibiotic STI prophylaxis in surveys from the UK, Australia and the Netherlands[2–6] — with comparable reported use among MSM living with HIV.[10] Notably, interest and acceptability for STI prophylaxis among MSM is much higher, ranging from 53% to 84% in surveys.[2 11] STI prophylaxis use has been found to be associated with higher risk behaviours, for example greater numbers of condomless sex partners and chemsex, and is also associated with STI diagnosis in the past 12 months.[3 4] Although the most commonly used antibiotic for STI prophylaxis is doxycycline, emerging evidence suggests causing syphilis, or meaningfully confirmed in *Chlamydia trachomatis*. However, high rates of tetracycline resistance in *Neisseria gonorrhoeae* already preclude treatment of gonorrhoea with doxycycline, and its use as prophylaxis is not likely to be effective in preventing gonorrhoea infection. Also of major concern is the potential for selection of resistance among potentially pathogenic bacterial flora such as *Staphylococcus aureus* and respiratory tract pathogens. Consideration also needs to be given to the impact on community prevalence of resistance determinants within commensal organisms, with higher prevalence purported among MSM populations.[12]

There remain key gaps in understanding the risk of AMR emergence with prophylactic doxycycline for STIs, as well as some of the facilitators and drivers that lead to individuals' decisions to self-source antibiotics. In addition to addressing the question of efficacy, some current trials examining doxycycline as STI prophylaxis will attempt to address aspects of AMR. In the interim, it is important clinicians ask about antibiotic STI prophylaxis use and discuss the limited benefits and potential risks. This position statement provides an update on the current available evidence and practical guidance for clinicians providing care to individuals reporting antibiotic STI prophylaxis use.

Handling editor Anna Maria Geretti

Twitter John Saunders @saunders_j

Contributors MK, NM, HF and JMS coauthored the updated position statement. MK wrote the first draft of the manuscript, and all other authors provided comments and edits.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; Internally peer reviewed.

OPEN ACCESS

- "Importantly, it remains the case that doxycycline taken as PEP or pre- exposure prophylaxis (PrEP) for STIs **is not endorsed** by BASHH or UKHSA"

- Kohli M, Medland N, Fifer H, Saunders J. BASHH updated position statement on doxycycline as prophylaxis for sexually transmitted infections. Sex Transm Infect. 2022;98(3):235-236. doi:10.1136/sextrans-2022-055425

Updated Australian Recommendations

2023 Consensus Statement on doxycycline prophylaxis (Doxy-PEP) for the prevention of syphilis, chlamydia and gonorrhoea among gay, bisexual, and other men who have sex with men in Australia.

- "Doxy-PEP should be considered **primarily for the prevention of syphilis** in GBMSM who are at risk of this STI, although for some individuals the reduction in chlamydia, and the lesser reduction of gonorrhoea might be important."
  - Some stakeholders held the view that **Doxy-PEP should be considered only for the prevention of syphilis** in GBMSM, for the reasons listed above

- https://ashm.org.au/about/news/doxy-pep-statement/#:~:text=infections%20(STI).-,Among%20gay%2C%20bisexual%2C%20and%20other%20men%20who%20have%20sex%20with,to%20varying%20levels%20of%20tetracycline

Updated Australian Recommendations

2023 Consensus Statement on doxycycline prophylaxis (Doxy-PEP) for the prevention of syphilis, chlamydia and gonorrhoea among gay, bisexual, and other men who have sex with men in Australia.

- GBMSM with a recent syphilis diagnosis
- GBMSM with two or more recent other (i.e., not syphilis) bacterial STI diagnoses
- GBMSM who identify an upcoming period of heightened STI risk, for example, attendance at a sex event, or holiday plans that likely involve sexual activity with multiple casual sexual partners
- GBMSM **with concurrent male and cisgender female sexual partners or other sexual partners with a uterus, recognising the additional health risks posed by chlamydia, gonorrhoea and syphilis for people with a uterus.**

- https://ashm.org.au/about/news/doxy-pep-statement/#:~:text=infections%20(STI).-,Among%20gay%2C%20bisexual%2C%20and%20other%20men%20who%20have%20sex%20with,to%20varying%20levels%20of%20tetracycline

Updated Australian Recommendations

2023 Consensus Statement on doxycycline prophylaxis (Doxy-PEP) for the prevention of syphilis, chlamydia and gonorrhoea among gay, bisexual, and other men who have sex with men in Australia.

- Given that STI risk is often not static, it is recommended to **use Doxy-PEP for a predefined period, e.g., 3–6 months, followed by review of the need for ongoing use**

- Doxy-PEP users should be assisted **to maximise the benefits of Doxy-PEP while minimising overall antibiotic use.**
  - For example, if a Doxy-PEP user tends to have multiple sexual partners during weekends but few during the week, then a single Monday morning dose of 200mg Doxy-PEP should adequately cover their STI risk, rather than multiple doses over the weekend

- https://ashm.org.au/about/news/doxy-pep-statement/#:~:text=infections%20(STI).-,Among%20gay%2C%20bisexual%2C%20and%20other%20men%20who%20have%20sex%20with,to%20varying%20levels%20of%20tetracycline

Kings County Guidance - Language is Important

Recommendations

1) Medical providers should **inform** cis-gender MSM and transgender women who have sex with men with a history of bacterial STI in the prior year about doxy-PEP, its efficacy, the potential benefits and risks of the intervention, and the alternative options available to prevent, diagnose, and treat STIs.
2) The decision to prescribe doxy-PEP should result from a **shared decision-making** process between the medical provider and the patient. Providers should give particular consideration to prescribing doxy-PEP to patients with a history of syphilis or a history of multiple STIs in the prior year. Providers may consider prescribing doxy-PEP on an episodic basis when patients anticipate periods when their risk of STI may be higher (e.g., group sex events).
3) Doxy-PEP is not recommended for cisgender women. A recent study found no effect of doxy-PEP in cisgender women in Kenya in preventing STIs.
4) The potential benefits and risks for transgender men (and other gender diverse patients assigned female sex at birth) who have anal sex with men are unknown. This population was not included in prior studies.
5) Counseling related to doxy-PEP should include the following elements:
    1. Evidence for the benefits of doxy-PEP.
    2. The known side effects and potential toxicities of doxycycline.
    3. The potential but unknown risks of doxy-PEP related to the microbiome and antibiotic resistance.
    4. How doxy-PEP should be taken and the need for ongoing monitoring.
    5. Alternatives to doxy-PEP.
6) Doxy-PEP should be provided as part of comprehensive sexual health services and patients should be supported to make decisions about the full spectrum of prevention options available to them, including HIV PrEP, HIV treatment for people living with HIV, condoms, HIV/STI testing and treatment, and vaccines.

1. Should inform
2. Cis-MSM and TGW with an STI in the prior year
3. Shared decision-making process
4. Important elements for counseling

- https://cdn.kingcounty.gov/-/media/depts/health/communicable-diseases/documents/hivstd/DoxyPEP-Guidelines.ashx

San Francisco- Language is Important

Recommendations

1. **Recommend doxy-PEP** to cis men and trans women who: 1) have had a bacterial STI in the past year and 2) report condomless anal or oral sexual contact with ≥ 1 cis male or trans female partner in the past year. These were the eligibility criteria used for the DoxyPEP study. Patients with a history of syphilis should be prioritized for doxy-PEP.

2. **Offer doxy-PEP using shared decision making** to cis men, trans men and trans women who report having multiple cis male or trans female sex partners in the prior year, even if they have not previously been diagnosed with an STI.

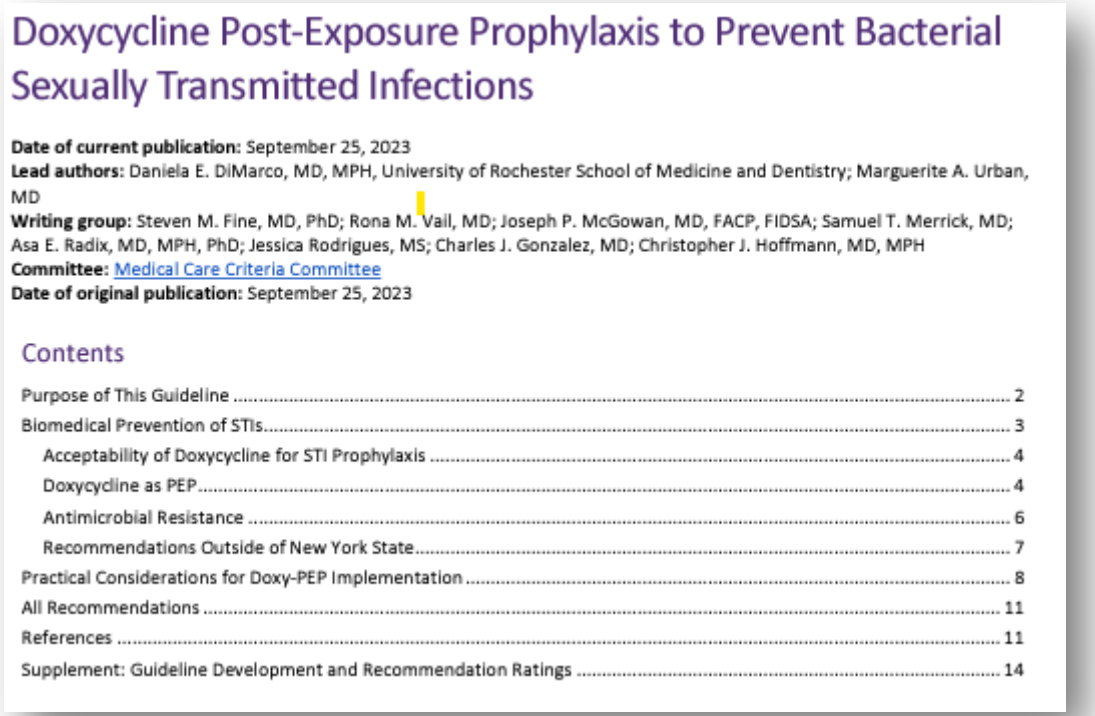
3. An ongoing randomized controlled trial in Kenya is assessing the safety and efficacy of doxy-PEP in cis women. **At this time, there is insufficient evidence to recommend doxy-PEP for STI prevention for individuals who report receptive vaginal sex.** If used in people who are able to become pregnant, pregnancy testing should be conducted as doxycycline use should be avoided during pregnancy.

1. Recommend
2. Offer

- https://www.sfcdcp.org/wp-content/uploads/2022/10/Health-Update-Doxycycline-Post-Exposure-Prophylaxis-Reduces-Incidence-of-Sexually-Transmitted-Infections-SFDPH-FINAL-10.20.2022.pdf

New York State Guidance

New York State Guidance



Doxycycline Post-Exposure Prophylaxis to Prevent Bacterial Sexually Transmitted Infections

Date of current publication: September 25, 2023
Lead authors: Daniela E. DiMarco, MD, MPH, University of Rochester School of Medicine and Dentistry; Marguerite A. Urban, MD
Writing group: Steven M. Fine, MD, PhD; Rona M. Vail, MD; Joseph P. McGowan, MD, FACP, FIDSA; Samuel T. Merrick, MD; Asa E. Radix, MD, MPH, PhD; Jessica Rodrigues, MS; Charles J. Gonzalez, MD; Christopher J. Hoffmann, MD, MPH
Committee: Medical Care Criteria Committee
Date of original publication: September 25, 2023

Contents

New York City Guidance

Pending

- https://www.hivguidelines.org/guideline/sti-doxy-pep/?mycollection=sexual-health

CDC Preliminary Guidance

- Should be considered

Box. Population recommended for consideration for use of doxycycline as PEP for bacterial STI prevention

Recommendation	Strength of recommendation and quality of evidence
• Doxycycline 200mg taken once orally within 72 hours of oral, vaginal or anal sex should be considered for gay, bisexual, and other men who have sex with men, and for transgender women, with a history of at least one bacterial STI (i.e. gonorrhea, chlamydia or syphilis) in the last 12 months.	**AI**
• No recommendation can be given at this time on the use of doxycycline PEP for cisgender women, cisgender heterosexual men, transgender men, other queer and nonbinary individuals. If this intervention is offered, it should be implemented with considerations for ancillary services detailed below.	**There is insufficient evidence to assess the balance of benefits and harms of the use of doxycycline PEP**

New York State Guidance

☑ RECOMMENDATIONS

Biomedical Prevention of STIs

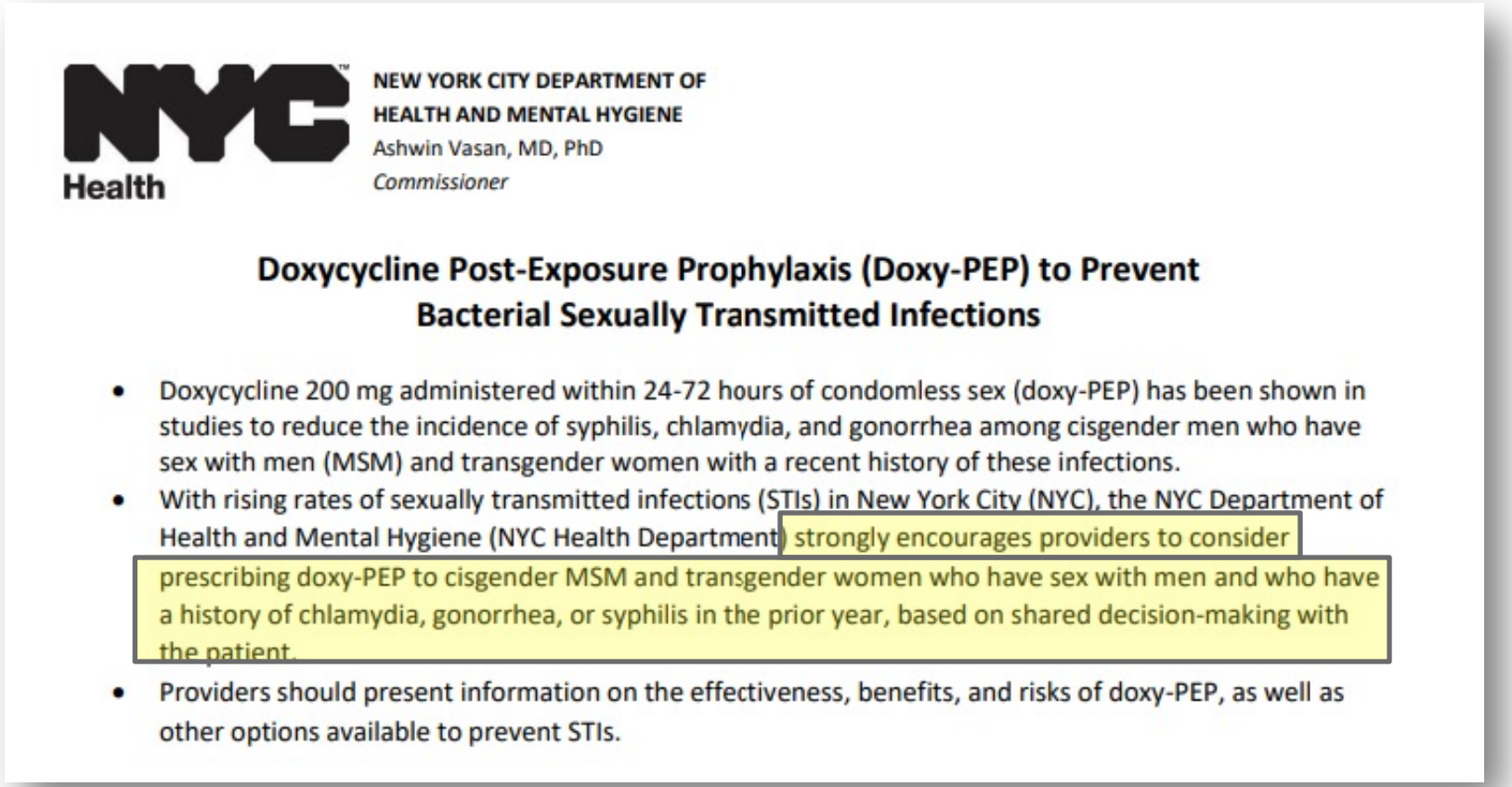
- Clinicians should offer doxy-PEP to cisgender men and transgender women who are taking HIV PrEP or receiving HIV care and 1) engage in condomless sex with partner(s) assigned male sex at birth and 2) have had a bacterial STI diagnosed within the past year and are at ongoing risk of STI exposure. (A1)
- Clinicians should offer doxy-PEP to cisgender men and transgender women who are *not* taking HIV PrEP or receiving HIV care and 1) engage in condomless sex with partner(s) assigned male sex at birth and 2) have had a bacterial STI diagnosed within the past year and are at ongoing risk of STI exposure. (A2†)
- Clinicians should engage in shared decision-making with cisgender men who 1) engage in condomless sex with multiple partners assigned female sex at birth and 2) have had a bacterial STI diagnosed within the past year, offering doxy-PEP on a case-by-case basis. (B3)
- When prescribing doxy-PEP, clinicians should use the dosing regimen of oral doxycycline 200 mg taken ideally within 24 to 72 hours of condomless sex (A1) and counsel patients (A*) on the key points for patient education outlined in Table 1: Considerations for Doxy-PEP Implementation.
- For individuals taking doxy-PEP, clinicians should screen for HIV, chlamydia, gonorrhea, and syphilis at least every 3 months. (A1)
- Clinicians should offer HIV PrEP to individuals who do not have HIV and are initiating or using doxy-PEP. (A*)
- Clinicians should offer HIV treatment to individuals with HIV who are not on antiretroviral therapy and are initiating or using doxy-PEP. (A1)

Abbreviations: doxy-PEP, doxycycline post-exposure prophylaxis; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection.

- Should offer to cis-men and TGW with an STI in the past year and ongoing exposure
- Shared decision making with cis-MSW

- https://www.hivguidelines.org/guideline/sti-doxy-pep/?mycollection=sexual-health

New York City Guidance



NEW YORK CITY DEPARTMENT OF
HEALTH AND MENTAL HYGIENE
Ashwin Vasan, MD, PhD
Commissioner

Doxycycline Post-Exposure Prophylaxis (Doxy-PEP) to Prevent Bacterial Sexually Transmitted Infections

- Doxycycline 200 mg administered within 24-72 hours of condomless sex (doxy-PEP) has been shown in studies to reduce the incidence of syphilis, chlamydia, and gonorrhea among cisgender men who have sex with men (MSM) and transgender women with a recent history of these infections.
- With rising rates of sexually transmitted infections (STIs) in New York City (NYC), the NYC Department of Health and Mental Hygiene (NYC Health Department) strongly encourages providers to consider prescribing doxy-PEP to cisgender MSM and transgender women who have sex with men and who have a history of chlamydia, gonorrhea, or syphilis in the prior year, based on shared decision-making with the patient.
- Providers should present information on the effectiveness, benefits, and risks of doxy-PEP, as well as other options available to prevent STIs.

- Strongly consider prescribing based on a shared-decision making approach

How Do I Provide Doxy-PEP?

Who Should I **Offer** Doxy-PEP To?

Populations
Cis-gender MSM
Transgender women
Cis-gender MSW
Cis-gender women

Vulnerability
2 STIs in Past 12 months
1 STI in past 12 months
Persons taking PrEP
0 STIs but non-monogamous condomless sex
Presenting for Care

How Do I Counsel Patient About Doxy-PEP Risks?

Side Effects

- Photosensitivity
- Pill esophagitis
- Gastrointestinal distress

Unknowns

- Antimicrobial resistance
- Microbiome changes
  - Weight gain

How Do I Prescribe Doxy-PEP?

FOR _____ DATE _____

ADDRESS _____

REFILL _____ TIMES

A generically equivalent drug product may be dispensed unless the practitioner hand writes the words "Brand Necessary" or "Brand Medically Necessary" on the face of the prescription.

℞

Doxycycline Monohydrate 100mg tabs
Take 2 tabs by mouth as needed every 24 hours
Take 2 capsules by mouth, once daily as needed (take within 72 hours of condomless sex),
Take no more then 2 capsules in any 24 hour period. Take with water and remain upright for 30 mins after taking
Dispense: #60 tabs
Refills: 0

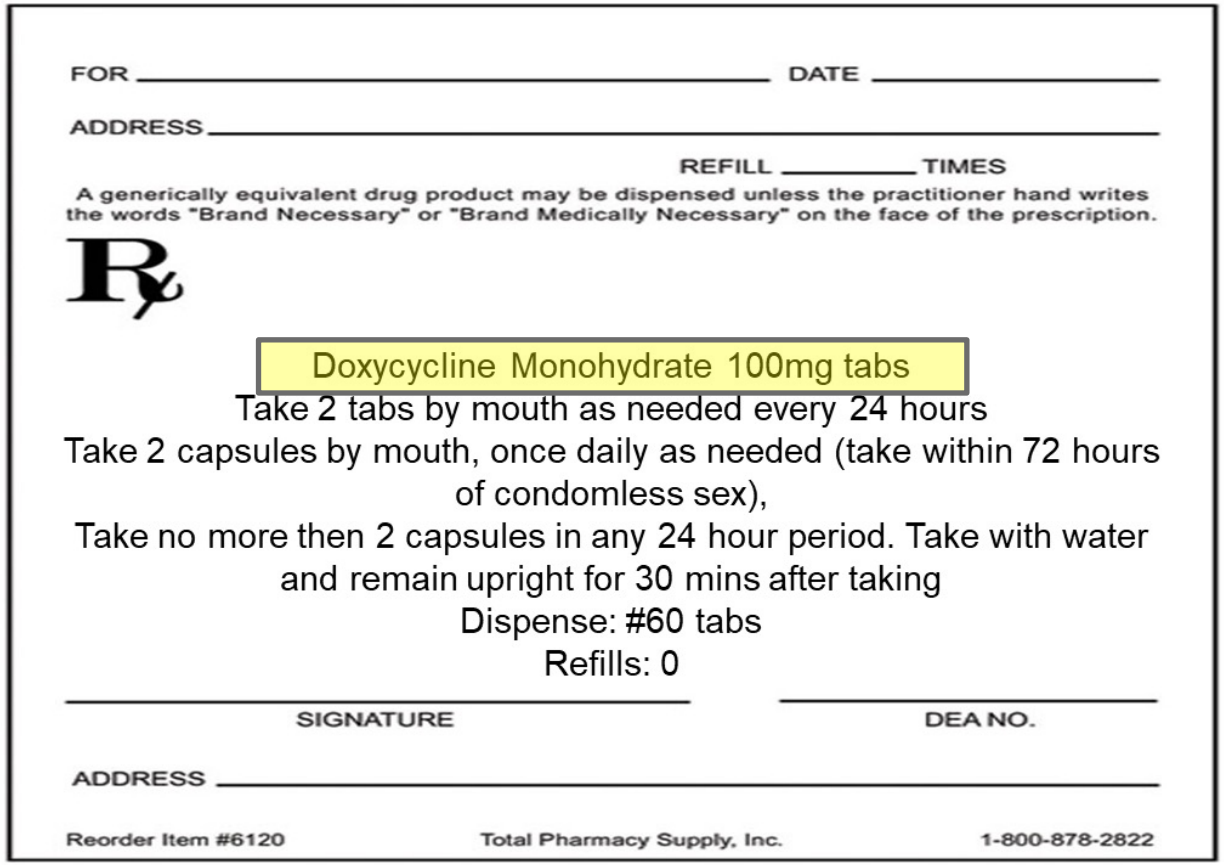
_____ _____

SIGNATURE DEA NO.

ADDRESS _____

Reorder Item #6120 Total Pharmacy Supply, Inc. 1-800-878-2822

How Do I Prescribe Doxy-PEP?



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℞

Doxycycline Monohydrate 100mg tabs

Take 2 tabs by mouth as needed every 24 hours

Take 2 capsules by mouth, once daily as needed (take within 72 hours of condomless sex),

Take no more then 2 capsules in any 24 hour period. Take with water and remain upright for 30 mins after taking

Dispense: #60 tabs

Refills: 0

_____ _____

SIGNATURE DEA NO.

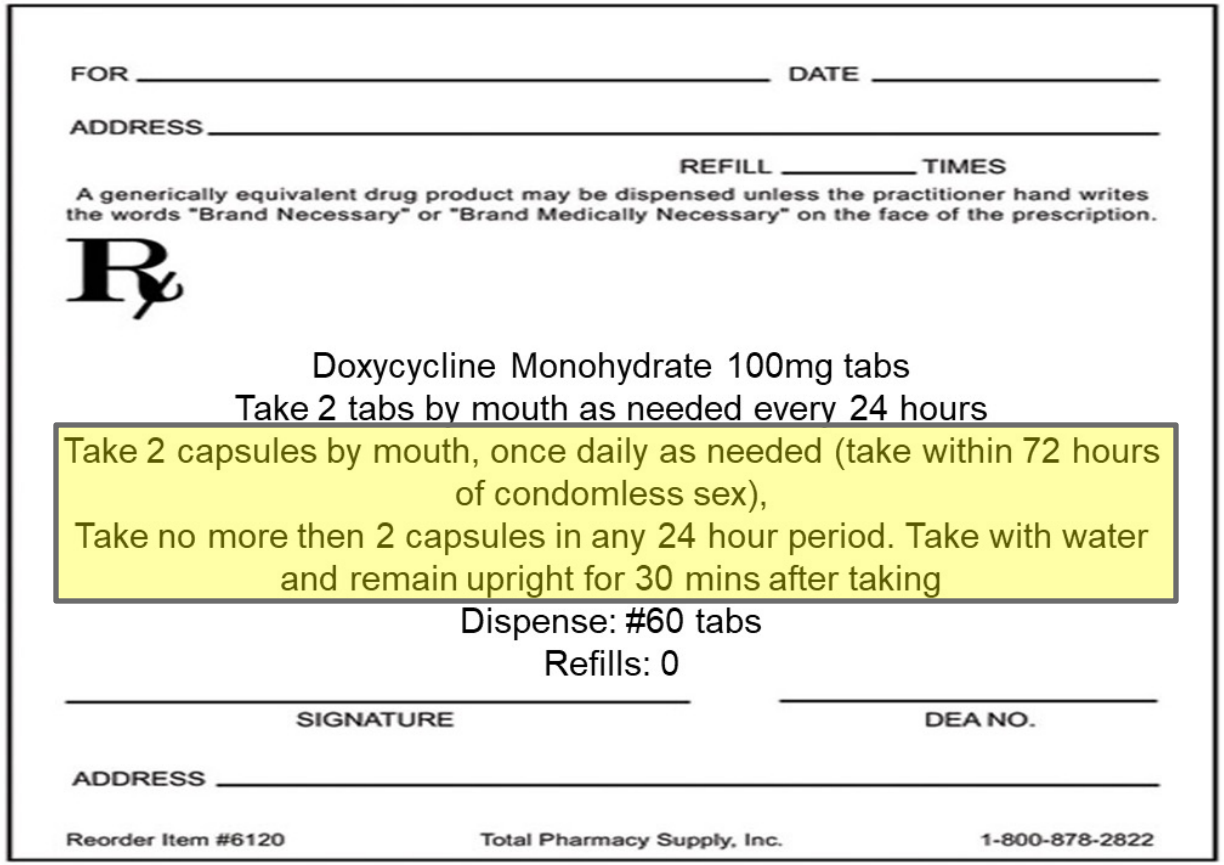
ADDRESS _____

Reorder Item #6120 Total Pharmacy Supply, Inc. 1-800-878-2822

Hyclate or Monohydrate

- Hyclate – cheaper
- Monohydrate – less GI distress

How Do I Prescribe Doxy-PEP?



FOR _____ DATE _____

ADDRESS _____

REFILL _____ TIMES

A generically equivalent drug product may be dispensed unless the practitioner hand writes the words "Brand Necessary" or "Brand Medically Necessary" on the face of the prescription.

℞

Doxycycline Monohydrate 100mg tabs
Take 2 tabs by mouth as needed every 24 hours

Take 2 capsules by mouth, once daily as needed (take within 72 hours of condomless sex),
Take no more then 2 capsules in any 24 hour period. Take with water and remain upright for 30 mins after taking

Dispense: #60 tabs
Refills: 0

_____ _____

SIGNATURE DEA NO.

ADDRESS _____

Reorder Item #6120 Total Pharmacy Supply, Inc. 1-800-878-2822

- Detailed instructions

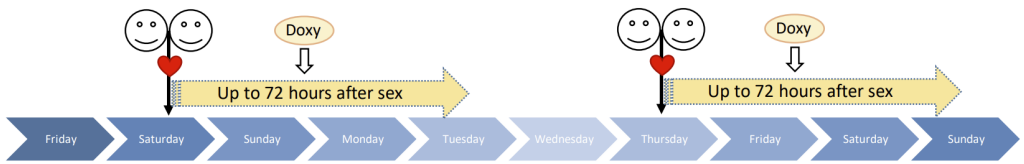
How Do I Prescribe Doxy-PEP?

Doxy PEP – How to Take

= sex without a condom, including oral sex

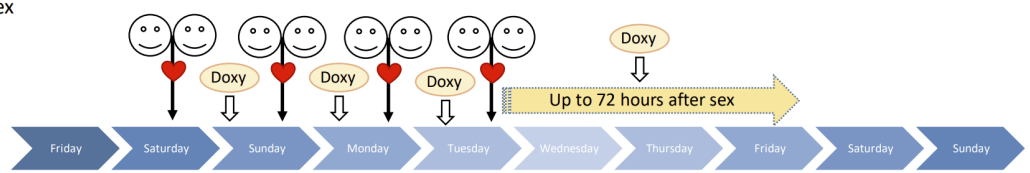
Two 100 mg pills of doxycycline ideally <u>within 24 hours</u> but no later than 72 hours after condomless oral, anal or vaginal sex

Example: Sex on Sat; take dose of doxy by Tues



Example: Sex on Thursday; take dose of doxy by Sunday

Example 2: Daily (or more) sex Sat-Tues; take daily dose of doxy and last dose within 24 hours *but not later than 72 hours* after last sex



***No more than* 200 mg every 24 hours**

About Doxy-PEP

What is doxy-PEP?

- Doxy-PEP means taking the antibiotic doxycycline after sex, to prevent getting an STI. It is like a morning-after pill but for STIs. Taking doxy-PEP reduces your chance of acquiring syphilis, gonorrhea, and chlamydia by about two-thirds.

When should I take doxy-PEP?

- Two 100 mg pills of doxycycline should be taken ideally within 24 hours but no later than 72 hours after condomless sex. Condomless sex means oral, anal or vaginal/front-hole sex where a condom isn't used for the entire time.

What about when I have sex again?

- If you have sex again within 24 hours of taking doxycycline, take another dose 24 hours after your last dose. You can take doxycycline as often as every day when you are having condomless sex but don't take more than 200 mg (two 100 mg pills) every 24 hours.

How should I take doxy-PEP?

- Take doxycycline with plenty of water or something else to drink so that it does not get stuck when you swallow. If your stomach is upset by doxycycline, taking it with food may help.
- Some people are more sensitive to the sun when they take doxycycline, so wear sunscreen.
- Please do not share doxycycline with others.
- Avoid dairy products, calcium, antacids, or multivitamins 2 hours before after taking doxycycline.

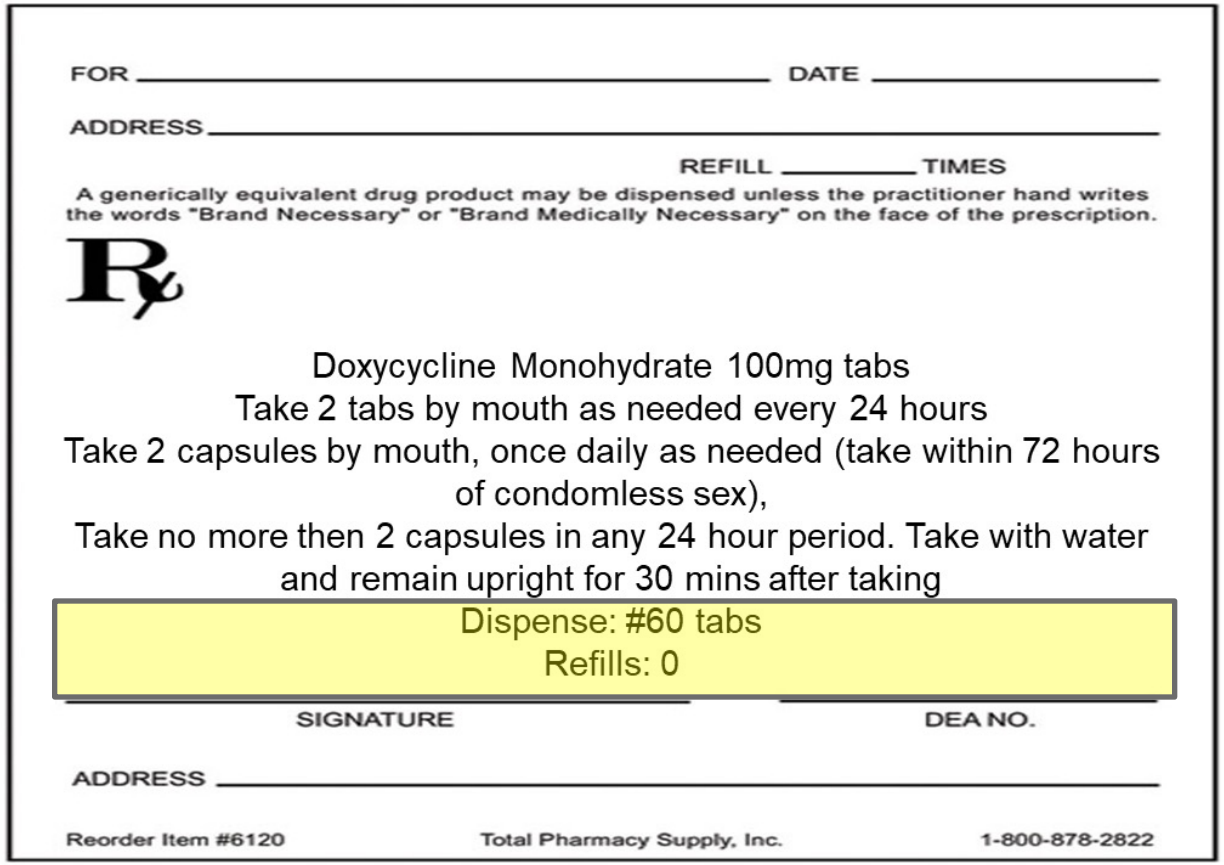
What are we still learning about doxy-PEP?

- Does it affect normal ("good") bacteria in our intestines?
- Could it increase or decrease the bacteria that live on our skin, or make them resistant to doxycycline (for example staph)?
- Will doxy-PEP increase doxycycline resistance in bacteria that cause STIs?
  - Although doxycycline has been used for decades, there is not resistance to doxycycline in chlamydia or syphilis.
  - About 25% of gonorrhea in the US is already resistant to doxy; doxy-PEP may not work against these strains. The DoxyPEP study and other studies will help understand whether using doxy-PEP changes resistance in gonorrhea.

Reminders

- Call us at 628-217-6692 if you run out of doxycycline, if you are having any side effects, or if you think you may have an STI.
- Please continue to get tested for STIs every 3 months and whenever you have symptoms.
- Doxy-PEP doesn't protect against MPX (monkeypox), HIV, or other viral infections

How Do I Prescribe Doxy-PEP?



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Dispense: #60 tabs
Refills: 0

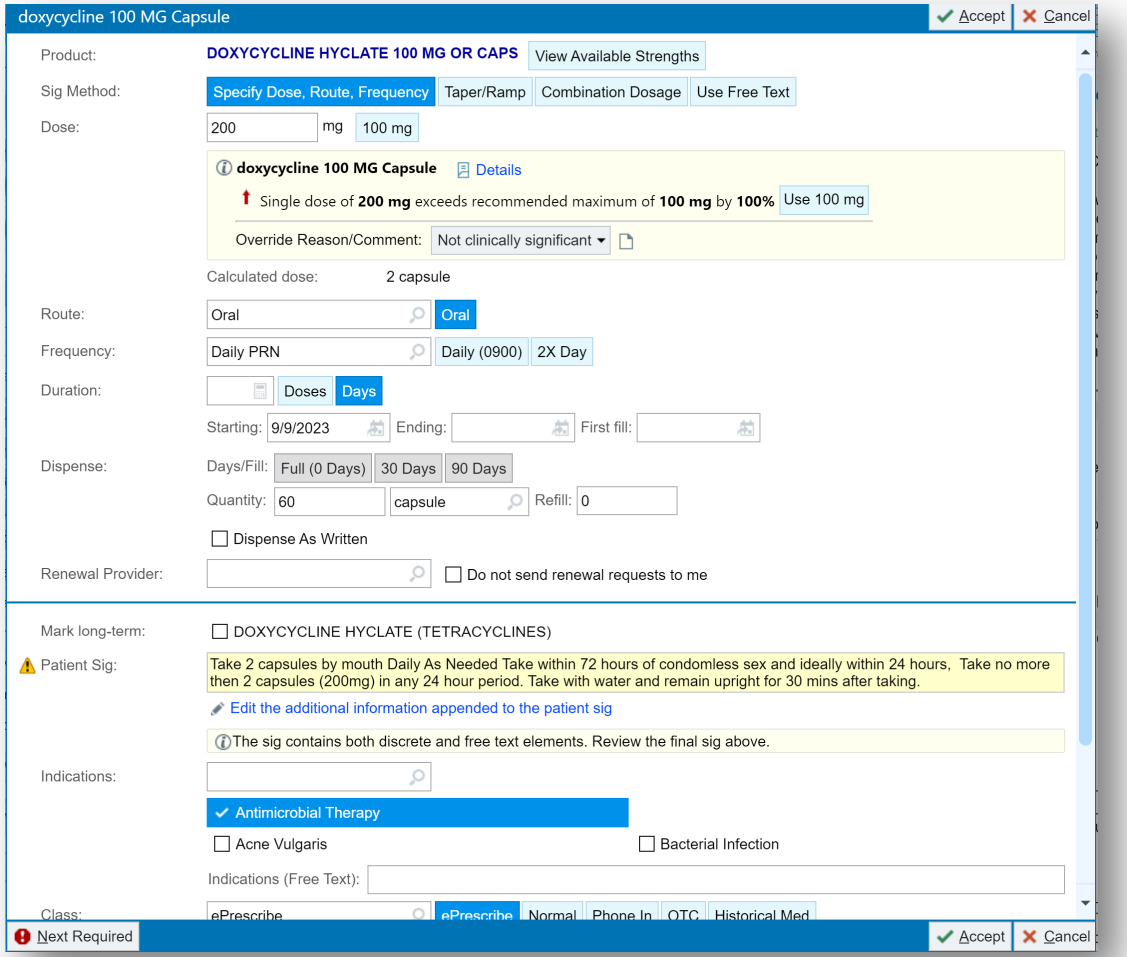
SIGNATURE _____ DEA NO. _____

ADDRESS _____

Reorder Item #6120 Total Pharmacy Supply, Inc. 1-800-878-2822

- Dispense and refills
- 25% of patients used >= 10 doses per month

How Do I Prescribe Doxy-PEP?



How Do I Follow Patients on Doxy-PEP?

Labs

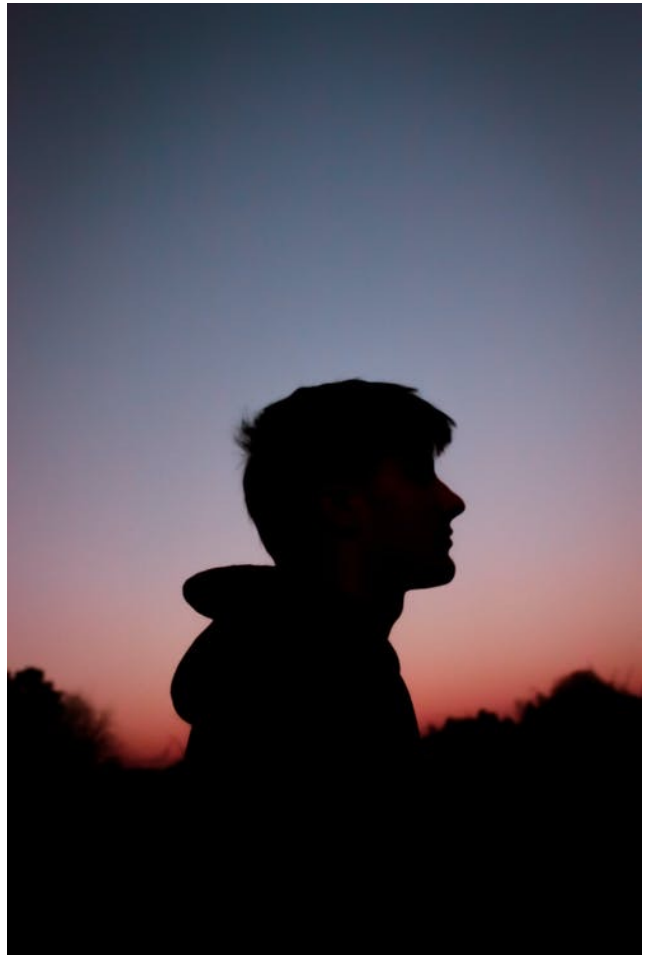
- Prior to initiation: None
  - Would not start on symptomatic patients
- Quarterly – STI testing
- Annually: CBC, LFTs, Creatinine

Treatment

- Treat as per the 2021 STI Guidelines
  - ***Consider in-person and exam and deferring empiric treatment for "exposure"***

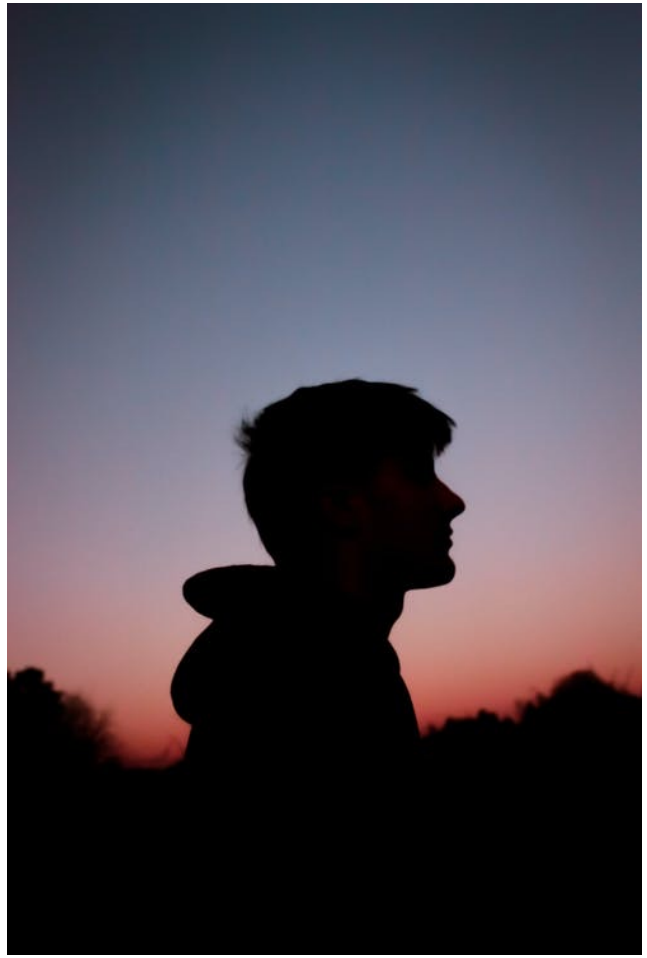
Igor

- Igor starts Doxy-PEP



Igor Comes Back

- Return to clinic 4 weeks later
- “It hurts when I pee, and I have a lot of green discharge”
- Labs repeated
  - Plus, gonorrhea culture
- Treated with Gentamicin and Azithromycin



Igor's Results

Lab results:
HIV Ab/Ag - Negative
Urine GC/CT – GC positive
Pharyngeal GC/CT – GC positive
Rectal GC/CT – negative
RPR – 1:16 - 1:128 – 10 weeks ago, 1:32 4 weeks ago

Igor's Gonorrhea Culture

Lab results:

Azithromycin – susceptible (MIC 0.125)

Ciprofloxacin – resistant (MIC 1)

Ceftriaxone – susceptible (MIC 0.016)

Cefixime – Susceptible (48mm)

Tetracycline – resistant (MIC 12)

Tetracycline Resistant Gonorrhea

- Will it work for prophylaxis?
- What else can you offer him?

Does 4CMenB Vaccine Prevent Gonorrhea?

ORIGINAL STUDY

Meningococcus B Vaccination Effectiveness Against *Neisseria gonorrhoeae* Infection in People Living With HIV: A Case-Control Study

Angelo Roberto Raccagni, MD, Laura Galli, MSc,† Vincenzo Spagnuolo, MD,† Elena Bruzzesi, MD,* Camilla Muccini, MD,† Simona Bossolasco, MD,† Martina Ranzenigo, MD,* Nicola Gianotti, MD,† Riccardo Lolatto, MSc,† Antonella Castagna, MD,*† and Silvia Nozza, MD†*

Background: We assessed the vaccination effectiveness (VE) of multicomponent meningococcal serogroup B (4CMenB) vaccine against gonorrhea among people living with HIV (PLWH) with a previous diagnosis of sexually transmitted infection.

Methods: Unmatched case-control study on men who have sex with men living with HIV, in care at San Raffaele Scientific Institute, Milan, Italy, with gonorrhea, syphilis, chlamydia, or anal human papillomavirus between July 2016 (beginning of 4CMenB vaccination) and February 2021 (date of freezing). For the analysis, cases were people with ≥1 gonorrhea infection since July 2016, and controls were people with ≥1 syphilis, chlamydia, or anal human papillomavirus infection since July 2016. Logistic regression was used to provide the estimate of 4CMenB VE against gonorrhea.

Results: Included people living with HIV were 1051 (103 cases, 948 controls); 349 of 1051 (33%) received 2 doses of 4CMenB vaccination. The median follow-up was 3.8 years (2.1–4.3 years). The unadjusted estimate for VE against gonorrhea was 42% (95% confidence interval, 6%–64%; $P = 0.027$). Logistic regression showed that VE against gonorrhea remained significant (44%; 95% confidence interval, 9%–65%; $P = 0.020$) after adjusting for some factors that might have a potential influence on VE or those with significant unbalanced distributions between cases and controls at univariable analysis.

However, the feasibility of developing a vaccine primarily targeting *Neisseria gonorrhoeae* has been historically questioned as all previous vaccine candidates failed at reducing gonorrhea cases. The high antigenic variability, the lack of natural protection following infection, and the ability to subvert the immune system are challenges for vaccine development.[4–6]

Although several gonococcal antigens showed promise in different preclinical stages, a new vaccine would be available for clinical use in several years.[7] Therefore, expanding the current indications of accessible vaccines might be the most effective solution in a short-term scenario. Antiserogroup B *Neisseria meningitidis* vaccines have been identified as the ideal candidate, after having demonstrated a cross-protective immune response.[8,9] Ecologic evidence from Cuba and Norway highlighted a possible reduction of cases after vaccination with outer-membrane vesicle (OMV)–based serogroup B antimeningococcal vaccines.[10,11] In New Zealand, MeNZB has shown to decrease both gonorrhea cases by 31% and gonococcal-related hospitalizations by 24%.[8,12,13] Currently, multicomponent meningococcal serogroup B (4CMenB) is the most used vaccine against serogroup B *N. meningitidis* worldwide. Recent evidence from the United States and Australia, by means of surveillance or medical records, supports its effectiveness against *N. gonorrhoeae*.[14–16] Moreover, given the additional

Effectiveness of a serogroup B outer membrane vesicle meningococcal vaccine against gonorrhoea: a retrospective observational study

Winston E Abara, Kyle T Bernstein, Felicia M T Lewis, Julia A Schillinger, Kristen Feemster, Preeti Pathela, Susan Hariri, Aras Islam, Michael Eberhart, Iris Cheng, Alexandra Ternier, Jennifer Sanderson Slutsker, Sarah Mbaeyi, Robbie Madera, Robert D Kirkcaldy

Summary

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Interpretation MenB-4C vaccination was associated with a reduced gonorrhoea prevalence. MenB-4C could offer cross-protection against *Neisseria gonorrhoeae*. Development of an effective gonococcal vaccine might be feasible with implications for gonorrhoea prevention and control.

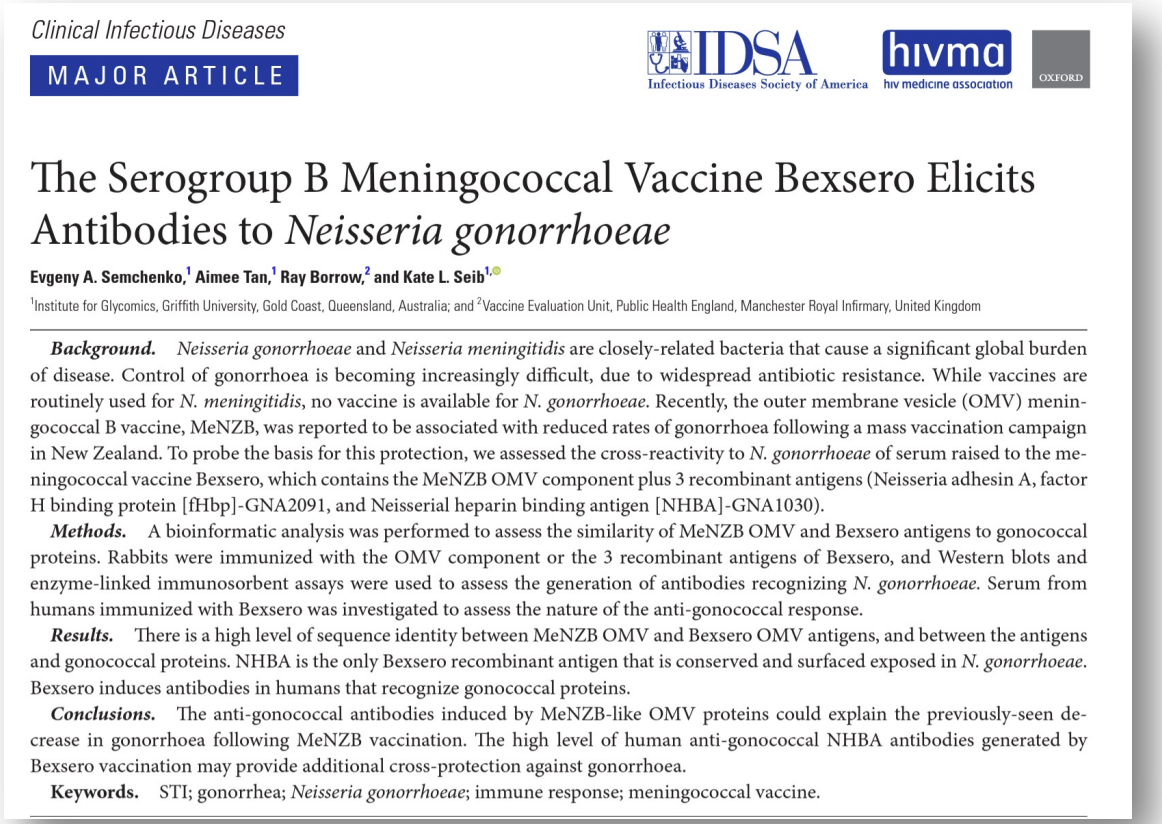
COLUMBIA | COLUMBIA UNIVERSITY IRVING MEDICAL CENTER

- Raccagni AR, Galli L, Spagnuolo V, et al. Meningococcus B Vaccination Effectiveness Against Neisseria gonorrhoeae Infection in People Living With HIV: A Case-Control Study. Sex Transm Dis. 2023;50(5):247-251. doi:10.1097/OLQ.0000000000001771
- Abara WE, Bernstein KT, Lewis FMT, et al. Effectiveness of a serogroup B outer membrane vesicle meningococcal vaccine against gonorrhoea: a retrospective observational study. Lancet Infect Dis. 2022;22(7):1021-1029. doi:10.1016/S1473-3099(21)00812-4

NEW YORK CITY STD HIV PREVENTION TRAINING CENTER

Why Would 4CMenB Prevent *N. Gonorrhea*

- Meningococcal serogroup B (MenB)-4C vaccine
  - 57 proteins were predicted to be surface expressed (outer membrane proteins [OMPs])
  - Majority of OMPs showed high sequence identity between the 2 bacterial species



Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

The Serogroup B Meningococcal Vaccine Bexsero Elicits Antibodies to *Neisseria gonorrhoeae*

Evgeny A. Semchenko,[1] Aimee Tan,[1] Ray Borrow,[2] and Kate L. Seib[1]

[1]Institute for Glycomics, Griffith University, Gold Coast, Queensland, Australia; and [2]Vaccine Evaluation Unit, Public Health England, Manchester Royal Infirmary, United Kingdom

Background. *Neisseria gonorrhoeae* and *Neisseria meningitidis* are closely-related bacteria that cause a significant global burden of disease. Control of gonorrhoea is becoming increasingly difficult, due to widespread antibiotic resistance. While vaccines are routinely used for *N. meningitidis*, no vaccine is available for *N. gonorrhoeae*. Recently, the outer membrane vesicle (OMV) meningococcal B vaccine, MeNZB, was reported to be associated with reduced rates of gonorrhoea following a mass vaccination campaign in New Zealand. To probe the basis for this protection, we assessed the cross-reactivity to *N. gonorrhoeae* of serum raised to the meningococcal vaccine Bexsero, which contains the MeNZB OMV component plus 3 recombinant antigens (Neisseria adhesin A, factor H binding protein [fHbp]-GNA2091, and Neisserial heparin binding antigen [NHBA]-GNA1030).

Methods. A bioinformatic analysis was performed to assess the similarity of MeNZB OMV and Bexsero antigens to gonococcal proteins. Rabbits were immunized with the OMV component or the 3 recombinant antigens of Bexsero, and Western blots and enzyme-linked immunosorbent assays were used to assess the generation of antibodies recognizing *N. gonorrhoeae*. Serum from humans immunized with Bexsero was investigated to assess the nature of the anti-gonococcal response.

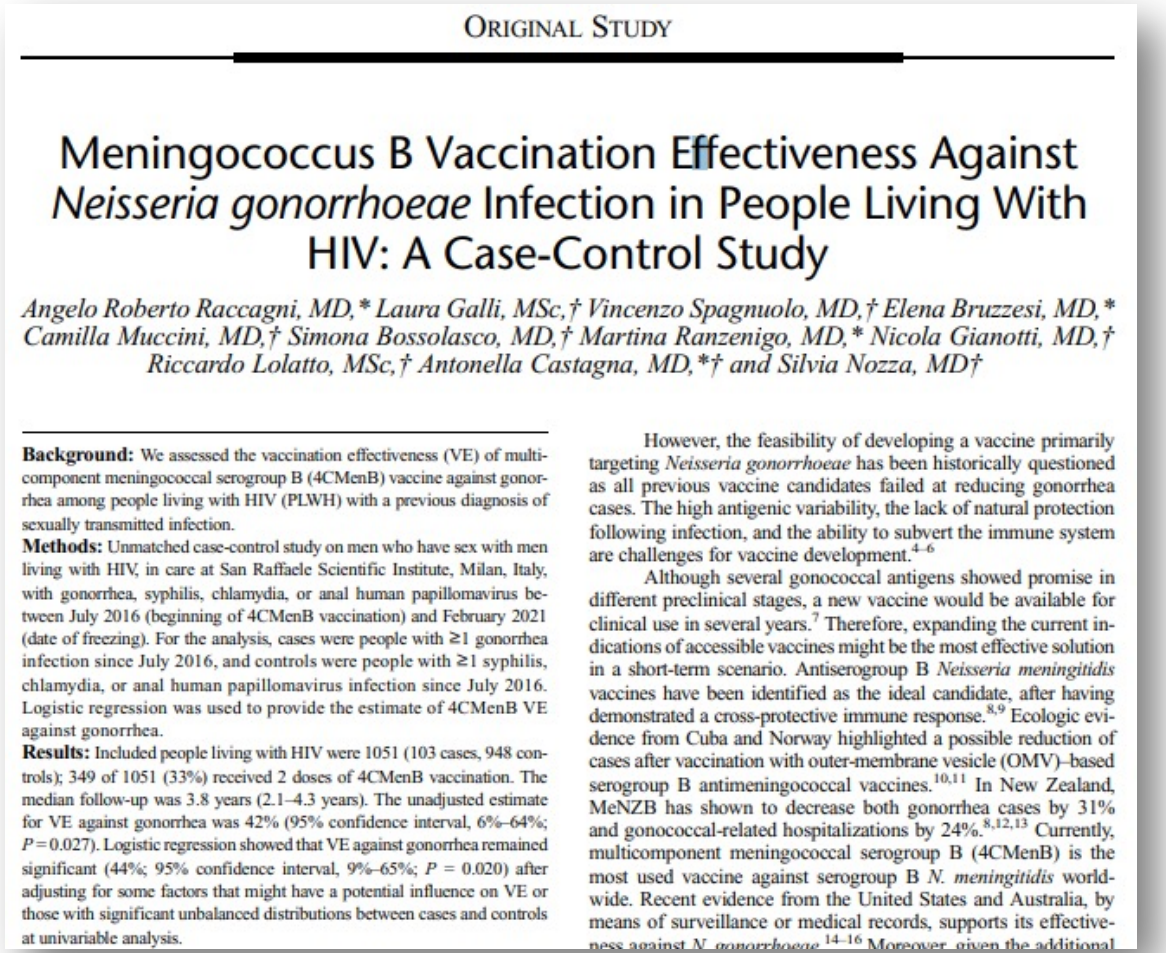
Results. There is a high level of sequence identity between MeNZB OMV and Bexsero OMV antigens, and between the antigens and gonococcal proteins. NHBA is the only Bexsero recombinant antigen that is conserved and surfaced exposed in *N. gonorrhoeae*. Bexsero induces antibodies in humans that recognize gonococcal proteins.

Conclusions. The anti-gonococcal antibodies induced by MeNZB-like OMV proteins could explain the previously-seen decrease in gonorrhoea following MeNZB vaccination. The high level of human anti-gonococcal NHBA antibodies generated by Bexsero vaccination may provide additional cross-protection against gonorrhoea.

Keywords. STI; gonorrhea; *Neisseria gonorrhoeae*; immune response; meningococcal vaccine.

- Evgeny A Semchenko, Aimee Tan, Ray Borrow, Kate L Seib, The Serogroup B Meningococcal Vaccine Bexsero Elicits Antibodies to Neisseria gonorrhoeae, Clinical Infectious Diseases, Volume 69, Issue 7, 1 October 2019, Pages 1101–1111, https://doi.org/10.1093/cid/ciy1061

Does 4CMenB Vaccine Prevent Gonorrhea?



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Design: Unmatched case-control study

Inclusion:

- **<u>MSM living with HIV</u>**
- Incident gonorrhea, syphilis, chlamydia, or anal human papillomavirus virus (HPV) between July 2016 and February 2021

Cases and Controls

- Cases: >= 1 gonorrhea infection
  - N = 103
- Controls >=1 syphilis, chlamydia, HPV infection
  - N = 948

Raccagni AR, Galli L, Spagnuolo V, et al. Meningococcus B Vaccination Effectiveness Against Neisseria gonorrhoeae Infection in People Living With HIV: A Case-Control Study. Sex Transm Dis. 2023;50(5):247-251. doi:10.1097/OLQ.0000000000001771

4CMenB Appears to Prevent Gonorrhea Infection

TABLE 3. Adjusted Odds Ratios for Gonorrhea Diagnosis

Characteristics	Adjusted Odds Ratio	95% Wald Confidence Limits		P
Age (≤44 vs. >44 y)	1.268	0.765	2.104	0.357
Years of ART (per 5 y longer)	0.736	0.591	0.917	**0.006**
$CD4^+$ (per 100 cells/μL higher)	0.946	0.877	1.020	0.146
$CD8^+$ (per 100 cells/μL higher)	0.975	0.932	1.021	0.286
HIV-RNA (<50 vs. ≥50 copies/mL)	0.708	0.386	1.297	0.264
HCV infection (positive vs. negative)	0.708	0.386	1.297	0.245
HCV infection (unknown vs. negative)	0.500	0.061	4.084	0.417
HBV infection (positive vs. negative)	1.822	0.846	3.926	0.358
HBV infection (unknown vs. negative)	1.576	0.887	2.800	0.647
4CMenB vaccination (Yes vs. No)	0.561	0.345	0.912	**0.020**

- Vaccine efficacy **44%** (9%-65%) after adjustment
- 4CMenB vaccination is associated with a lower risk of gonorrhea in MSM with HIV

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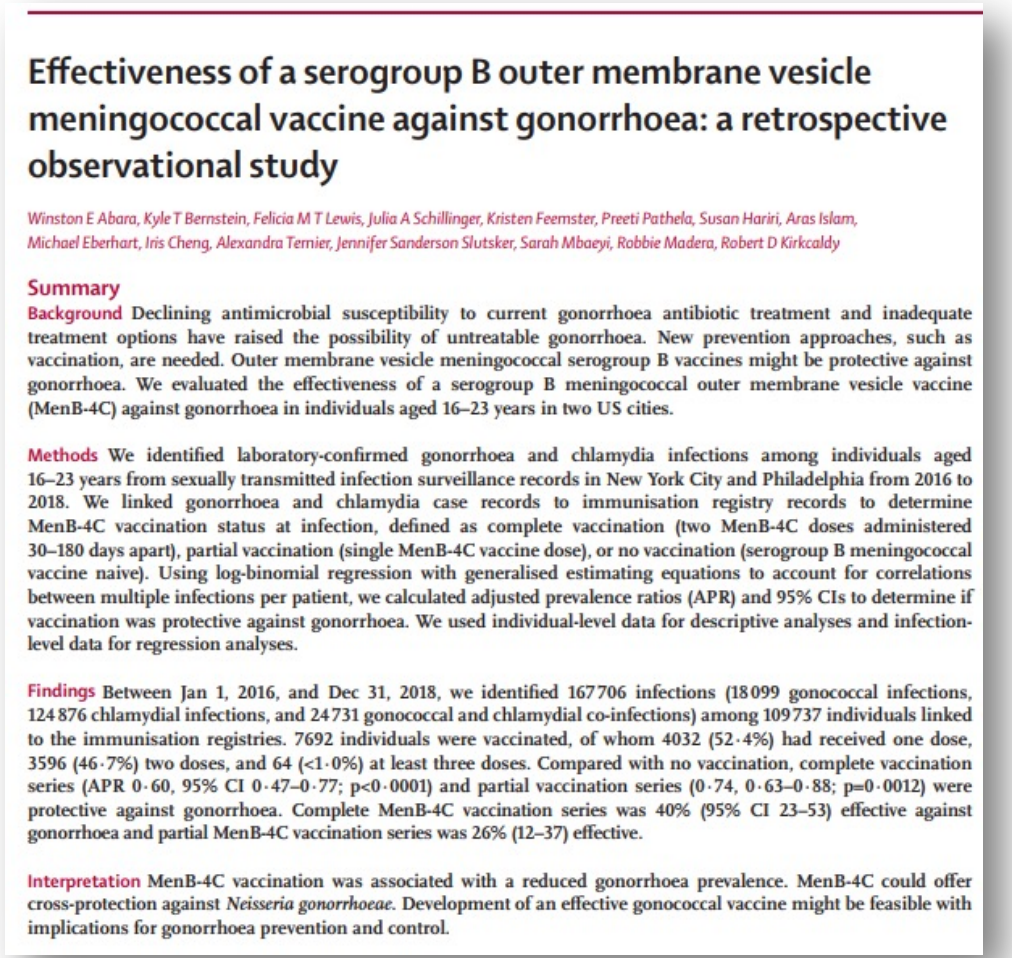

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Summary

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Methods We identified laboratory-confirmed gonorrhoea and chlamydia infections among individuals aged 16–23 years from sexually transmitted infection surveillance records in New York City and Philadelphia from 2016 to 2018. We linked gonorrhoea and chlamydia case records to immunisation registry records to determine MenB-4C vaccination status at infection, defined as complete vaccination (two MenB-4C doses administered 30–180 days apart), partial vaccination (single MenB-4C vaccine dose), or no vaccination (serogroup B meningococcal vaccine naive). Using log-binomial regression with generalised estimating equations to account for correlations between multiple infections per patient, we calculated adjusted prevalence ratios (APR) and 95% CIs to determine if vaccination was protective against gonorrhoea. We used individual-level data for descriptive analyses and infection-level data for regression analyses.

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Interpretation MenB-4C vaccination was associated with a reduced gonorrhoea prevalence. MenB-4C could offer cross-protection against *Neisseria gonorrhoeae*. Development of an effective gonococcal vaccine might be feasible with implications for gonorrhoea prevention and control.

Design: Case-Control Study

Inclusion:

- Diagnosed with gonorrhea or chlamydia
- 2016-2018
- **Age 16-23**
- Included in the immunization registry in NYC or Philadelphia

Cases and Controls (N = 109, 737)

- Cases: Gonorrhea infection
- Controls: Chlamydia infection

Abara WE, Bernstein KT, Lewis FMT, et al. Effectiveness of a serogroup B outer membrane vesicle meningococcal vaccine against gonorrhoea: a retrospective observational study. Lancet Infect Dis. 2022;22(7):1021-1029. doi:10.1016/S1473-3099(21)00812-4

4CMenB Appears to Prevent Gonorrhea Infection

	Gonorrhoea				Gonorrhoea and chlamydia co-infection			
	UPR (95% CI)	p value	APR (95% CI)	p value	UPR (95% CI)	p value	APR (95% CI)	p value
MenB-4C vaccination status								
Complete vaccination*	0·64 (0·51–0·79)	<0·0001	0·60 (0·47–0·77)	<0·0001	0·90 (0·70–1·17)	0·44	0·85 (0·64–1·13)	0·28
Partial vaccination†	0·83 (0·72–0·96)	0·0204	0·74 (0·63–0·88)	0·0012	1·15 (0·97–1·37)	0·11	1·06 (0·88–1·28)	0·56
Unvaccinated‡	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..
Race or ethnicity								
Black, non-Hispanic	0·94 (0·88–1·01)	0·11	0·81 (0·61–1·09)	0·17	1·40 (1·24–1·57)	<0·0001	1·39 (1·23–1·56)	<0·0001
Hispanic	0·69 (0·63–0·74)	<0·0001	0·72 (0·66–0·78)	<0·0001	0·86 (0·75–0·97)	0·0117	0·88 (0·77–1·01)	0·0700
Other§	0·97 (0·86–1·08)	0·54	0·97 (0·86–1·09)	0·60	1·32 (1·11–1·59)	0·0031	1·34 (1·11–1·60)	0·0018
White, non-Hispanic	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..
Gender								
Male	2·67 (2·58–2·76)	<0·0001	2·64 (2·58–2·80)	<0·0001	2·12 (2·01–2·23)	<0·0001	2·11 (1·98–2·24)	<0·0001
Female	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..
Jurisdiction								
New York City, NY, USA	0·75 (0·72–0·77)	<0·0001	1·03 (0·99–1·08)	0·13	0·72 (0·68–0·76)	<0·0001	0·99 (0·94–1·06)	0·91
Philadelphia, PA, USA	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..

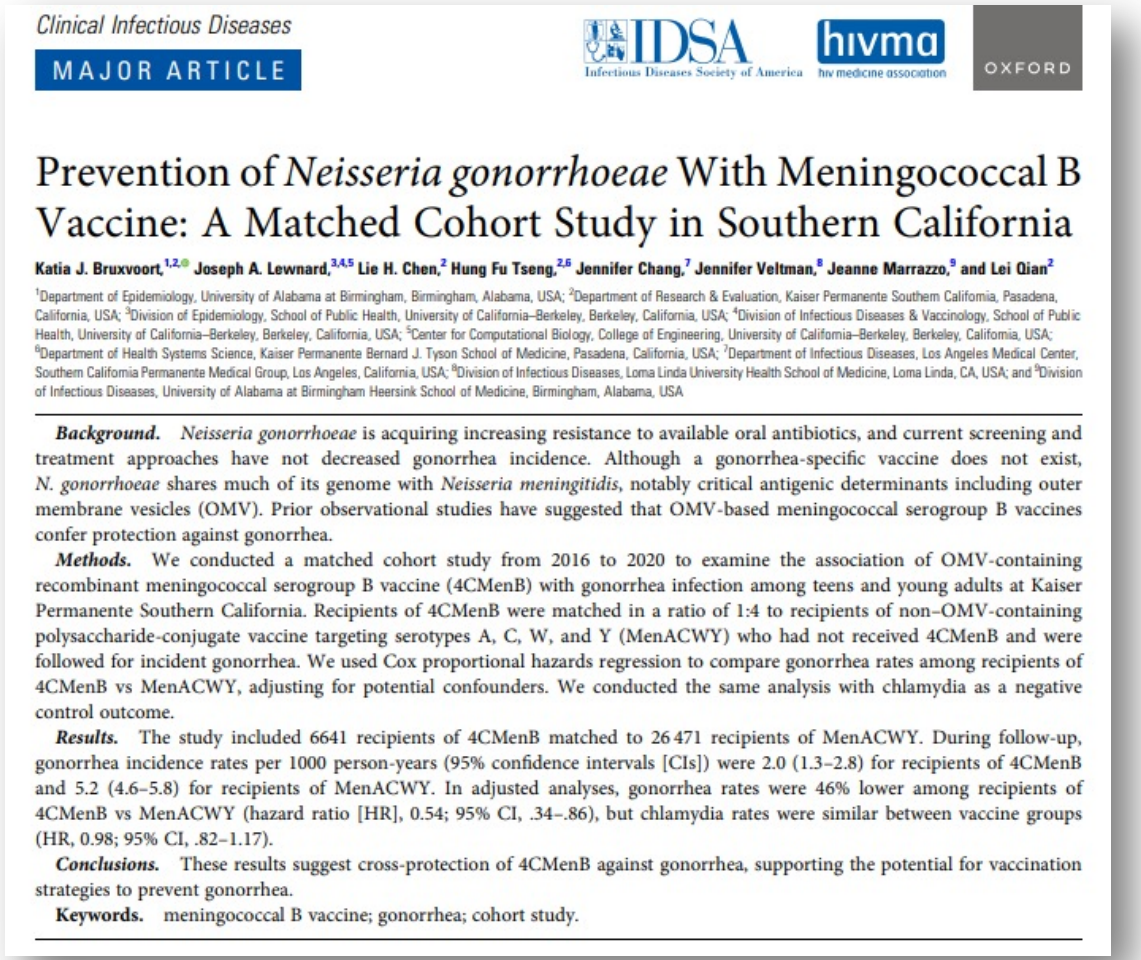
APR=adjusted prevalence ratio. UPR=unadjusted prevalence ratio. *Receipt of two doses of MenB-4C vaccine separated by 30–180 days. †Receipt of one MenB-4C dose. ‡Never vaccinated against *Neisseria meningitidis* serogroup B with MenB-4C or MenB-FHbp (ie, MenB vaccine naive or sexually transmitted infections occurred before first MenB-4C vaccine dose). §Asian, American Indian, Native Hawaiian or Pacific Islander, other race, or two or more races.

Table 2: **Association between MenB-4C vaccination and gonorrhoea or gonorrhoea and chlamydia co-infection compared with chlamydia**

- Complete MenB-4C vaccination series was **40%** (95% CI 23–53) effective against gonorrhea
- Partial MenB-4C vaccination series was **26%** (12–37) effective against gonorrhea

Abara WE, Bernstein KT, Lewis FMT, et al. Effectiveness of a serogroup B outer membrane vesicle meningococcal vaccine against gonorrhoea: a retrospective observational study. Lancet Infect Dis. 2022;22(7):1021-1029. doi:10.1016/S1473-3099(21)00812-4

4CMenB Appears to Prevent Gonorrhea Infection



Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Prevention of *Neisseria gonorrhoeae* With Meningococcal B Vaccine: A Matched Cohort Study in Southern California

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Background. *Neisseria gonorrhoeae* is acquiring increasing resistance to available oral antibiotics, and current screening and treatment approaches have not decreased gonorrhea incidence. Although a gonorrhea-specific vaccine does not exist, *N. gonorrhoeae* shares much of its genome with *Neisseria meningitidis*, notably critical antigenic determinants including outer membrane vesicles (OMV). Prior observational studies have suggested that OMV-based meningococcal serogroup B vaccines confer protection against gonorrhea.

Methods. We conducted a matched cohort study from 2016 to 2020 to examine the association of OMV-containing recombinant meningococcal serogroup B vaccine (4CMenB) with gonorrhea infection among teens and young adults at Kaiser Permanente Southern California. Recipients of 4CMenB were matched in a ratio of 1:4 to recipients of non–OMV-containing polysaccharide-conjugate vaccine targeting serotypes A, C, W, and Y (MenACWY) who had not received 4CMenB and were followed for incident gonorrhea. We used Cox proportional hazards regression to compare gonorrhea rates among recipients of 4CMenB vs MenACWY, adjusting for potential confounders. We conducted the same analysis with chlamydia as a negative control outcome.

Results. The study included 6641 recipients of 4CMenB matched to 26 471 recipients of MenACWY. During follow-up, gonorrhea incidence rates per 1000 person-years (95% confidence intervals [CIs]) were 2.0 (1.3–2.8) for recipients of 4CMenB and 5.2 (4.6–5.8) for recipients of MenACWY. In adjusted analyses, gonorrhea rates were 46% lower among recipients of 4CMenB vs MenACWY (hazard ratio [HR], 0.54; 95% CI, .34–.86), but chlamydia rates were similar between vaccine groups (HR, 0.98; 95% CI, .82–1.17).

Conclusions. These results suggest cross-protection of 4CMenB against gonorrhea, supporting the potential for vaccination strategies to prevent gonorrhea.

Keywords. meningococcal B vaccine; gonorrhea; cohort study.

Design: Matched Cohort Study

Inclusion:

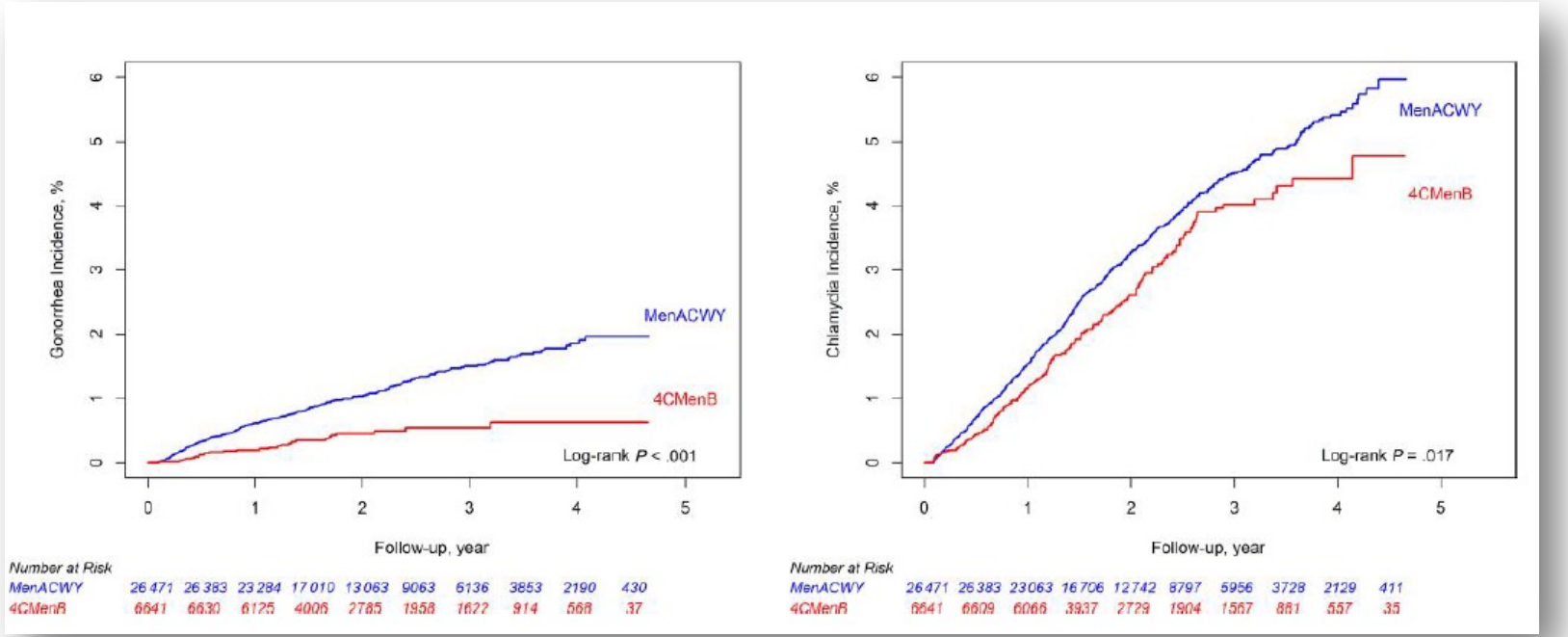
- Matched 1:4 to recipients of MenACWY.
- **Teens and Young Adults**

Cases and Controls (N = 6,641)

- Cases: Gonorrhea infection
- Controls: Chlamydia infection

Bruxvoort KJ, Lewnard JA, Chen LH, et al. Prevention of Neisseria gonorrhoeae With Meningococcal B Vaccine: A Matched Cohort Study in Southern California [published correction appears in Clin Infect Dis. 2023 Jan 11;:]. Clin Infect Dis. 2023;76(3):e1341-e1349. doi:10.1093/cid/ciac436

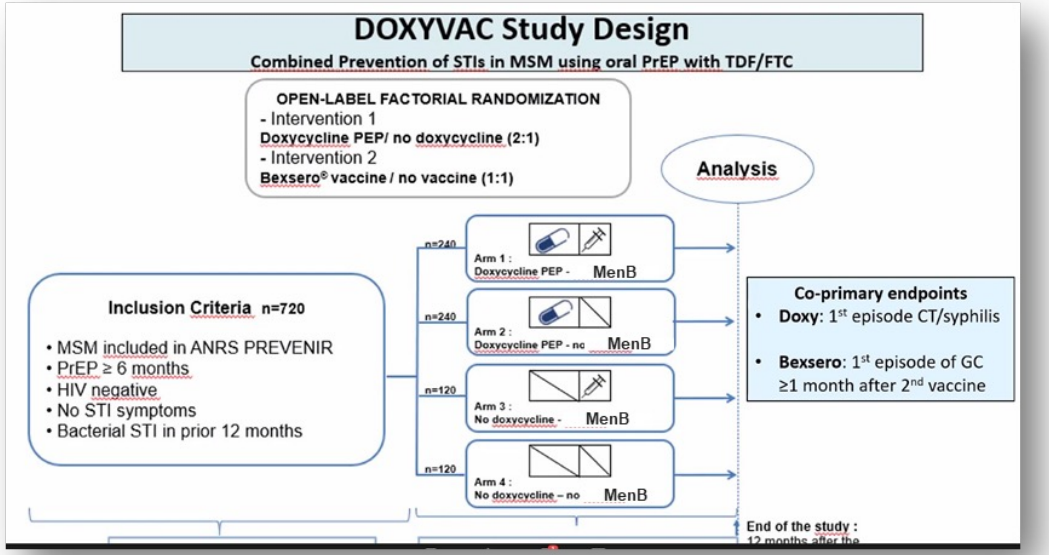
4CMenB Appears to Prevent Gonorrhea Infection



- Gonorrhea rates were **46%** lower among recipients of 4CMenB vs MenACWY
  - (HR, 0.54; 95% CI, .34–.86)
- Chlamydia rates were similar between vaccine groups
  - (HR, 0.98; 95% CI, .82–1.17).

- Bruxvoort KJ, Lewnard JA, Chen LH, et al. Prevention of Neisseria gonorrhoeae With Meningococcal B Vaccine: A Matched Cohort Study in Southern California [published correction appears in Clin Infect Dis. 2023 Jan 11;:]. Clin Infect Dis. 2023;76(3):e1341-e1349. doi:10.1093/cid/ciac436

DoxyVac Study – CROI 2023

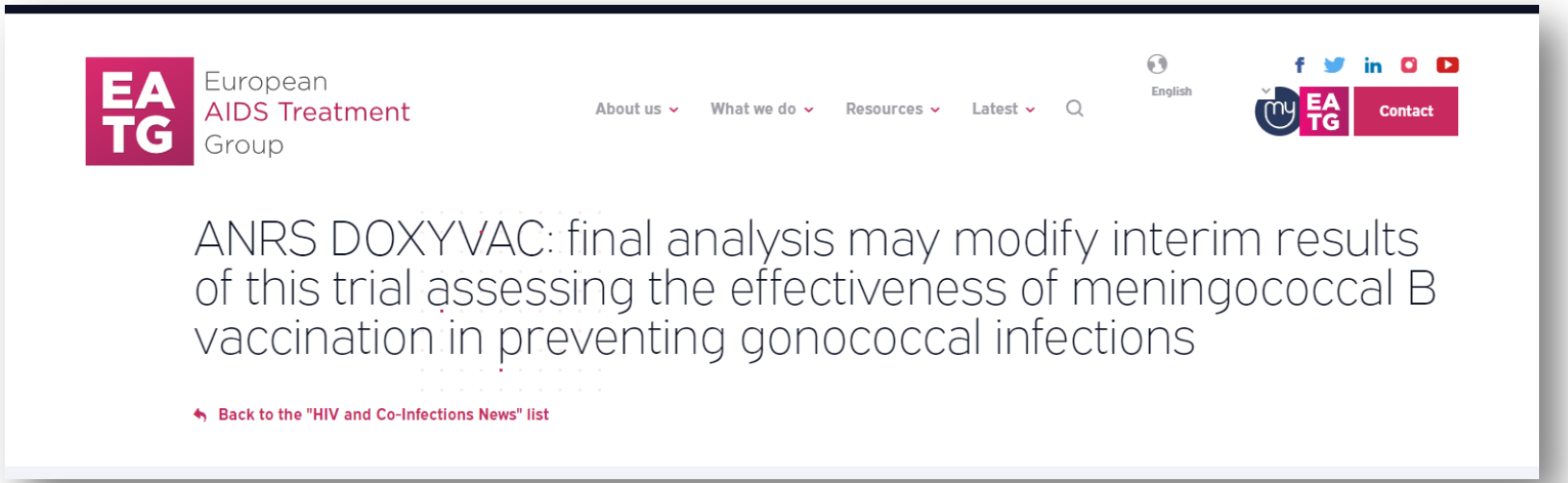


- Interim analysis
  - Incidence of first episode of gonorrhea: 9.8 vs 19.7 per 100 person years in the 4CmenB vaccine vs no vaccine arms
  - (aHR, 0.49; 95% CI, 0.27-0.88)

- DSMB recommended to stop the study and that all the participants be offered doxycycline and/or the meningococcal B vaccine

- Molina et al DOXYVAC CROI 2023 Abstract 119
- Liu AY, Buchbinder SP. CROI 2023: Epidemiologic Trends and Prevention for HIV and Other Sexually Transmitted Infections. Top Antivir Med. 2023;31(3):468-492.

Does MenB Vaccination Prevent Gonorrhea?



- Discrepancy between interim and final analysis on the effectiveness of the meningococcal B vaccine on gonococcal infections

- **Re-analysis is ongoing**

STI Prevention Summary

- We are in an era of STI prevention choice and patients should be aware of their options
- Doxy-PEP
  - Doxy-PEP **works** to prevent STIs in men who have sex with men and transgender women living with and without HIV
  - Doxy-PEP **does not work** to prevent STIs in persons born female
  - There remain unknowns about the overall impact, risks, and unintended consequences of Doxy-PEP that potential users should be aware of (**Shared Decision Making**)
- 4CMenB vaccine **MAY** reduce an individual's risk of gonorrhea
  - 4CMenB vaccination prevents against gonorrhea in observational studies, but randomized clinical trial data is **not confirmatory**
- Flexibility is key, management will change as we learn more
- **Research is needed to help us better understand the risks and benefits of STI prevention**

Thank You

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NYP Sexual Health Program

Providers

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- Al Cohall
- Eddie Perez
- Jacob McLean

Coordinators

- Angelica Arache
- Brian Simpson
- Emma Molina
- Josh Klein

Additional Resources

National STD Curriculum

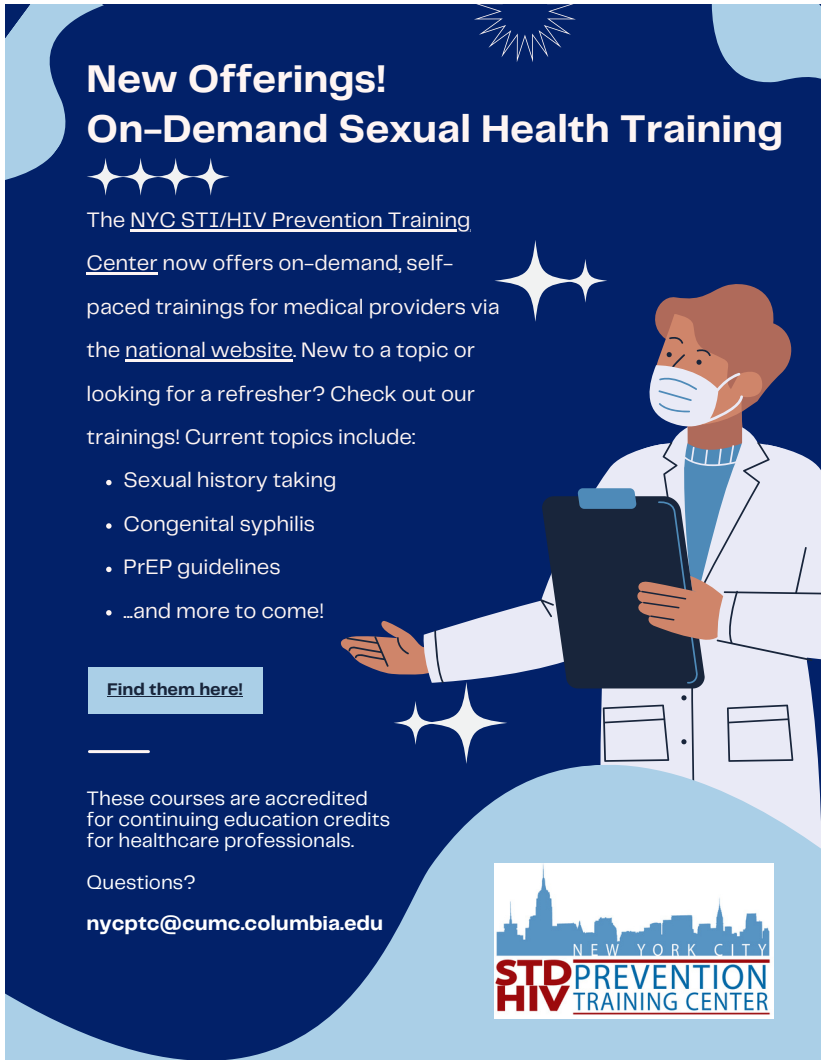
www.std.uw.edu

The *National STD Curriculum* is reviewing and updating content to align with CDC's 2021 STI Treatment Guidelines. Updated content will then launch as 2nd Edition. The free site addresses the diagnosis, treatment, and prevention of STDs and STIs.

- Seven self-study Lessons
- Question Bank topics with board-review style questions
- Podcast series on innovative and significant topics
- A learning group tool for healthcare entities to enroll members, assign units, and track progress
- FREE CME credits, CNE, and CE contact hours, and pharmacology CE for advanced practice nurses

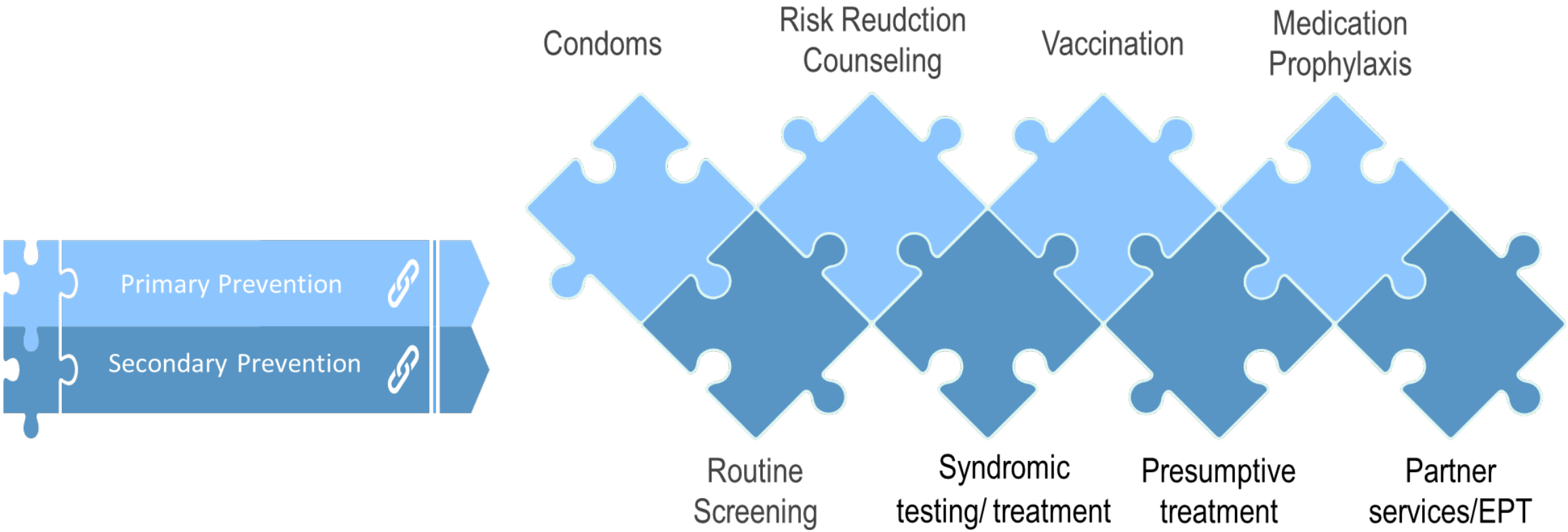
STDCCN.org

Sexual Health E-Learning Courses



- Interactive asynchronous online courses now available through the national site: https://courses.nnptc.org/eLearning.html
- Free and CE-accredited
- Interested? Check out our current courses and stay tuned for future topics!

Questions


Primary Prevention
Secondary Prevention
Condoms
Risk Reudction Counseling
Vaccination
Medication Prophylaxis
Routine Screening
Syndromic testing/ treatment
Presumptive treatment
Partner services/EPT