Medication Prophylaxis

Medication Prophylaxis

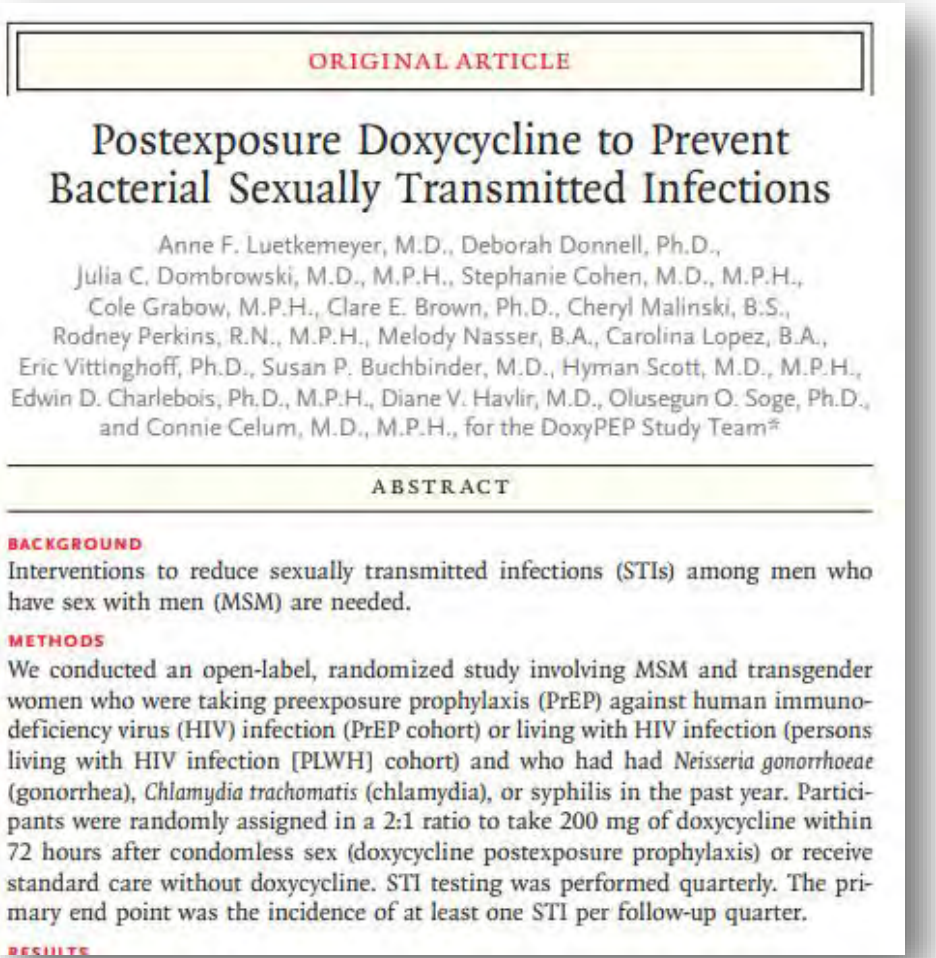
1. HIV post-exposure prophylaxis (PEP)
2. HIV pre-exposure prophylaxis (PrEP)
3. **Doxy-PEP**

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.

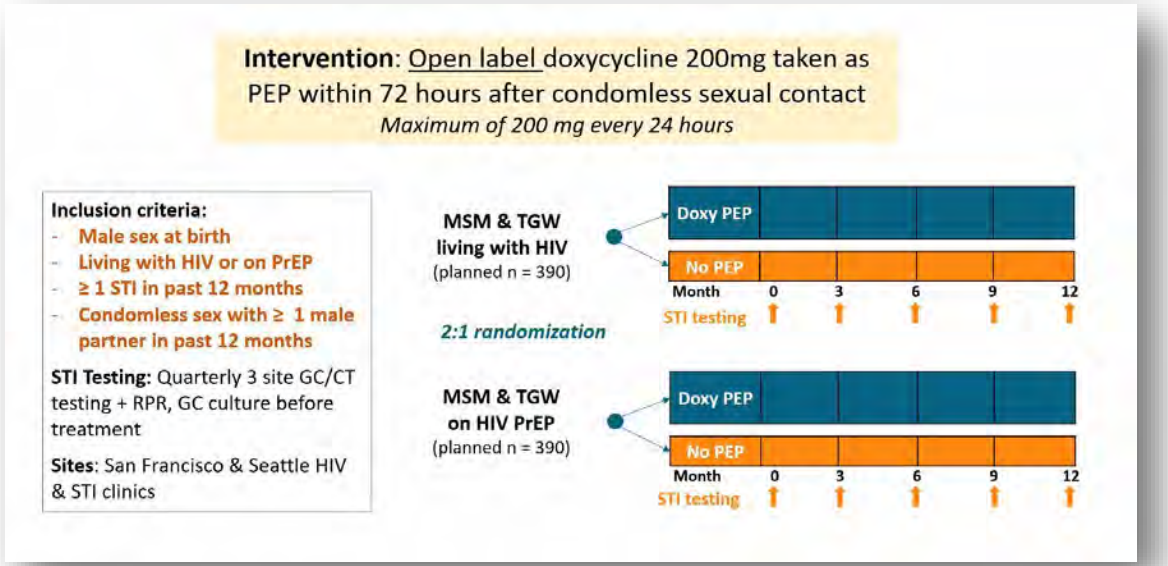
METHODS

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

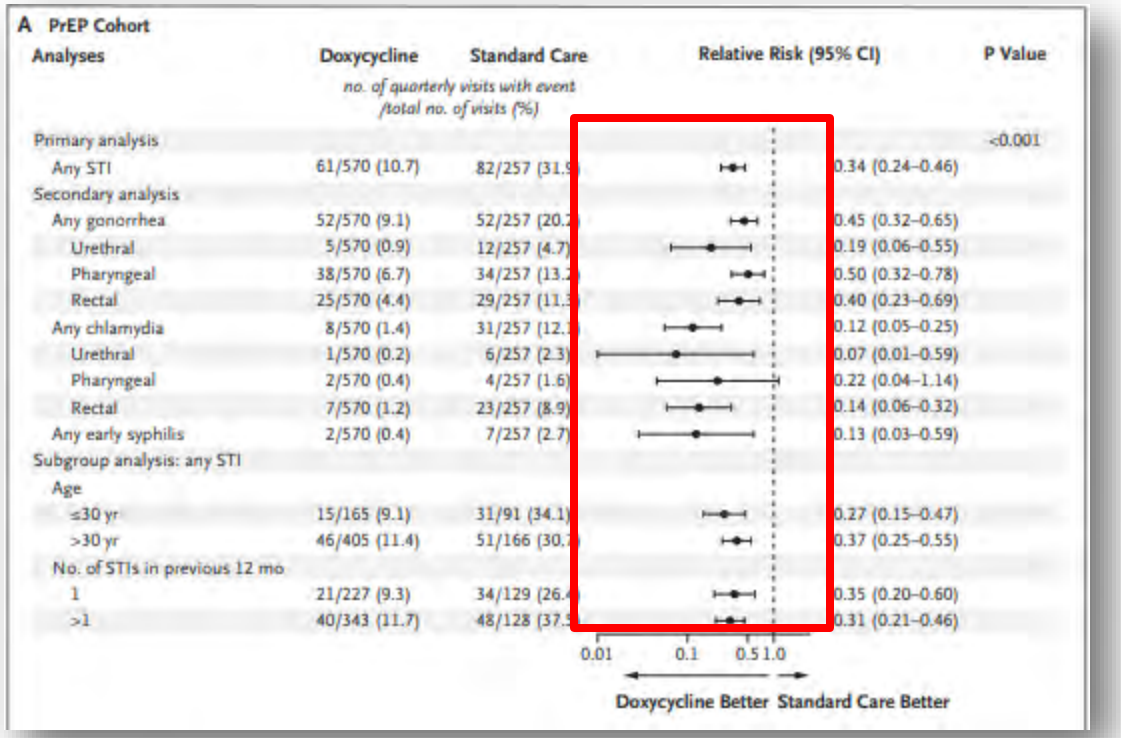


- **Design:** Multicenter, open-label, randomized, controlled, trial
- **Inclusion**
  - Men who have sex with men or Transgender women
  - Taking HIV PrEP or Living with HIV
  - Bacterial STI (chlamydia, gonorrhea, syphilis) in the past 12 months
  - Condomless sex with ≥ 1 male partner in past 12 months
- **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



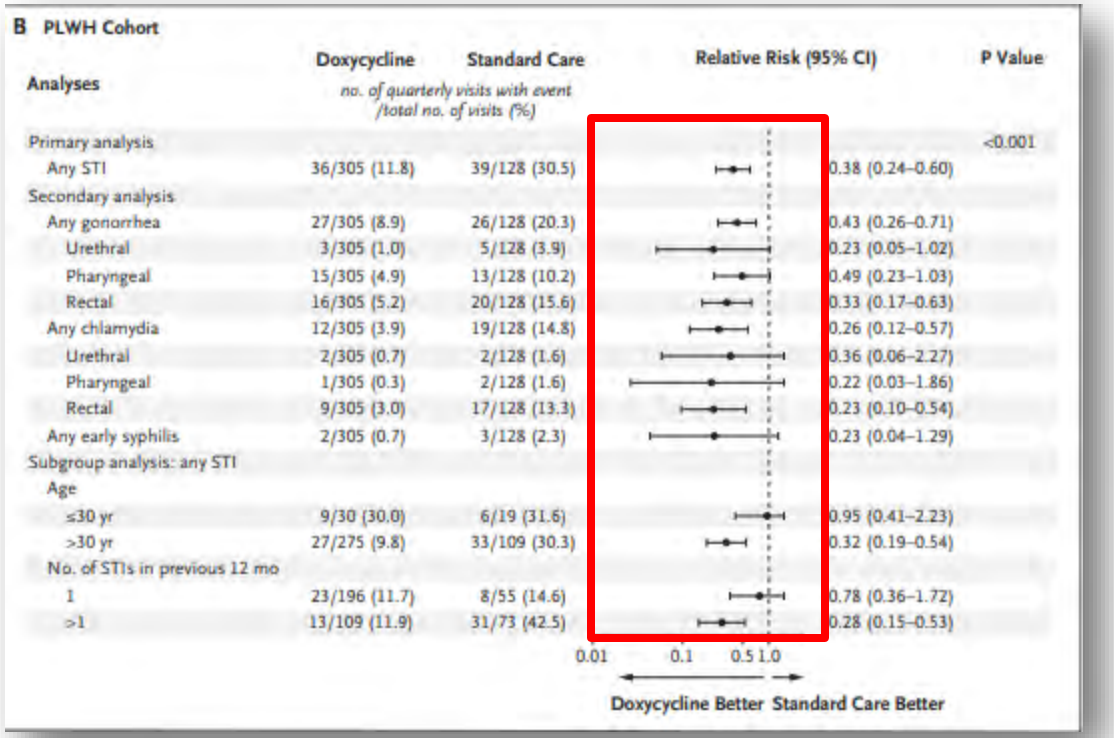
A PrEP Cohort

Analyses	Doxycycline	Standard Care	Relative Risk (95% CI)	P Value
	no. of quarterly visits with event /total no. of visits (%)			
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	Standard Care	Relative Risk (95% CI)	P Value
	no. of quarterly visits with event /total no. of visits (%)			
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

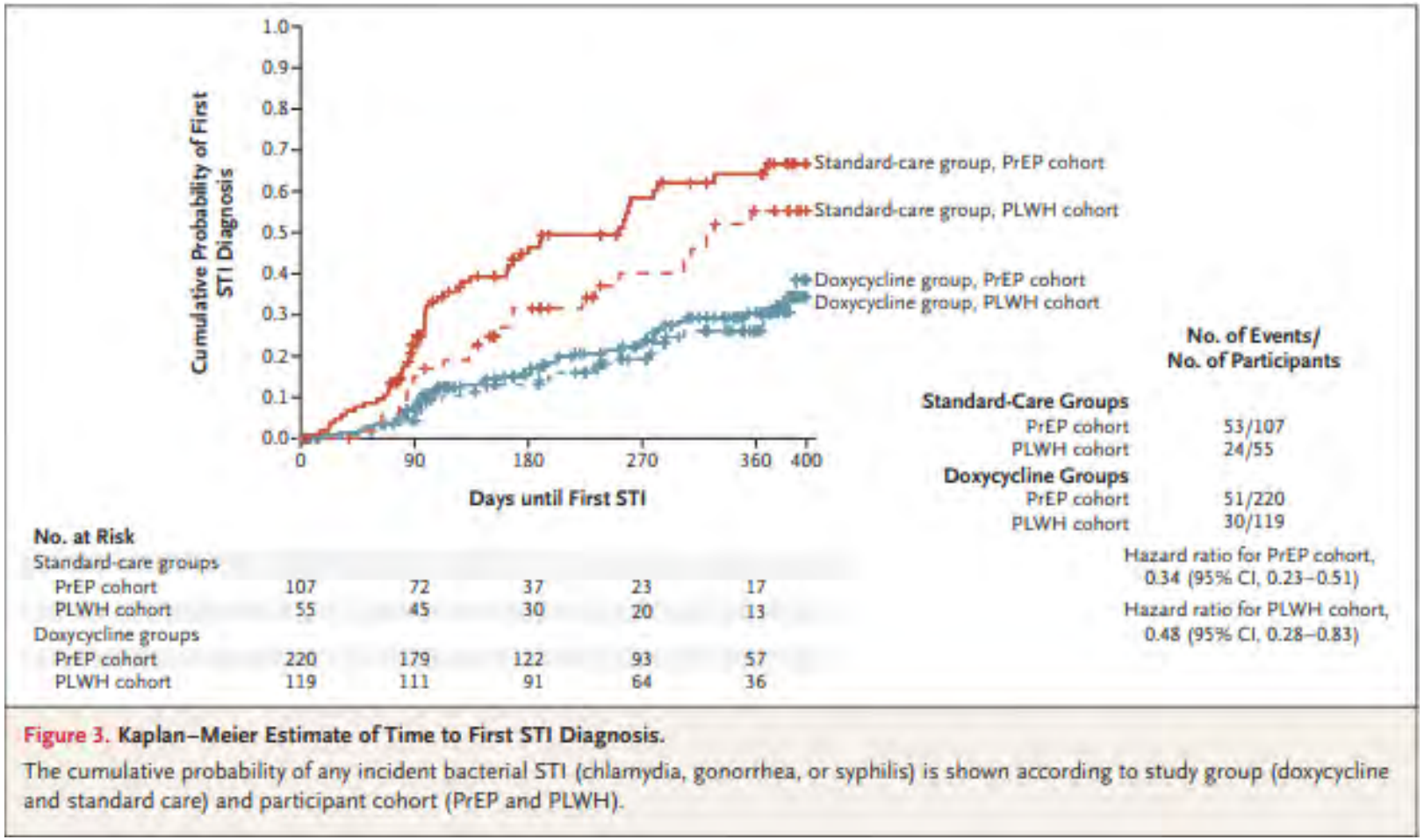


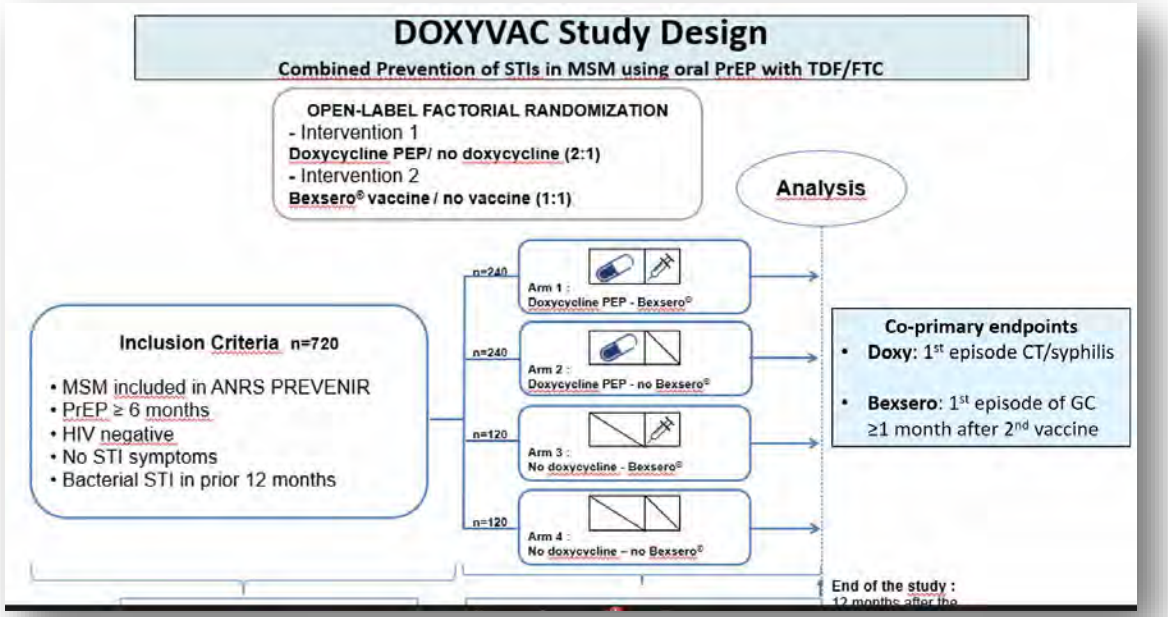
Figure 3. Kaplan–Meier Estimate of Time to First STI Diagnosis.

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

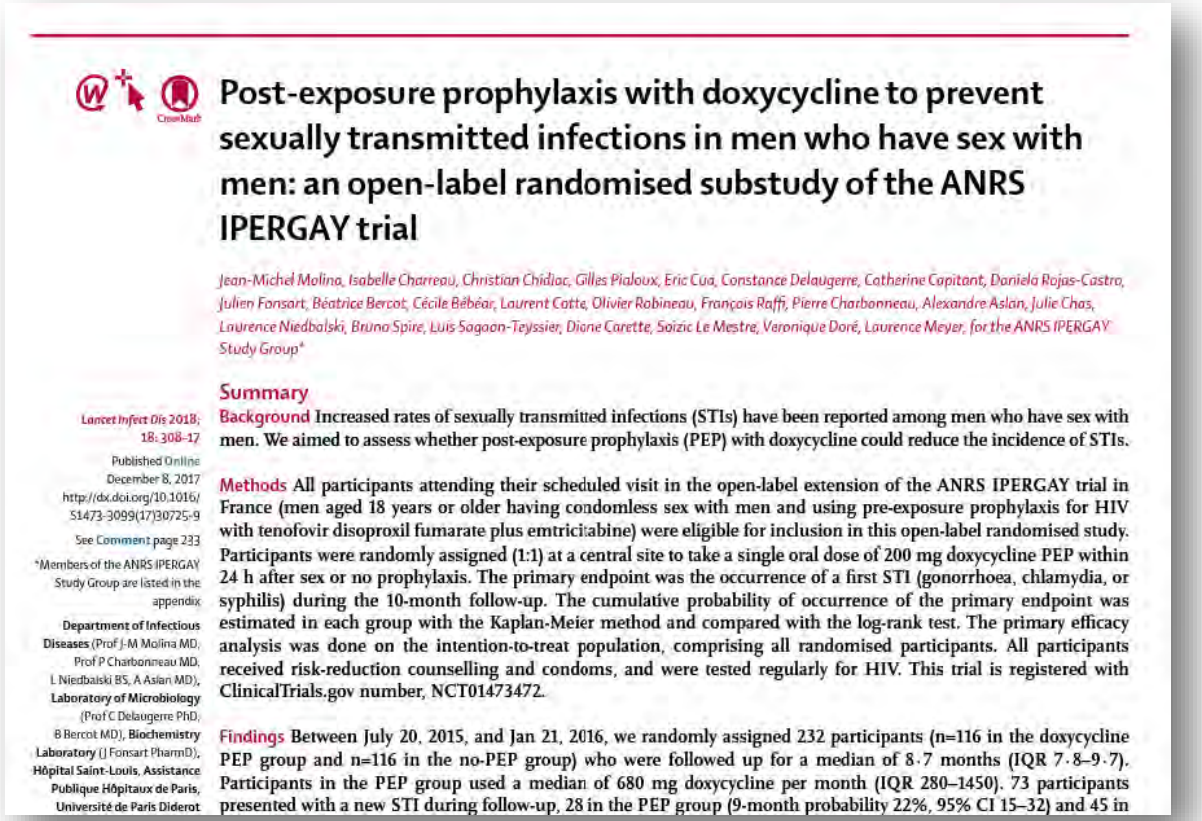
DoxyVac Trial



- **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 JM, Bercot B, Assoumou L, et al. Doxycycline prophylaxis and meningococcal group B vaccine to prevent bacterial sexually transmitted infections in France (ANRS 174 DOXYVAC): a multicentre, open-label, randomised trial with a 2 × 2 factorial design. Lancet Infect Dis. 2024;24(10):1093-1104. doi:10.1016/S1473-3099(24)00236-6

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, Diane 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.

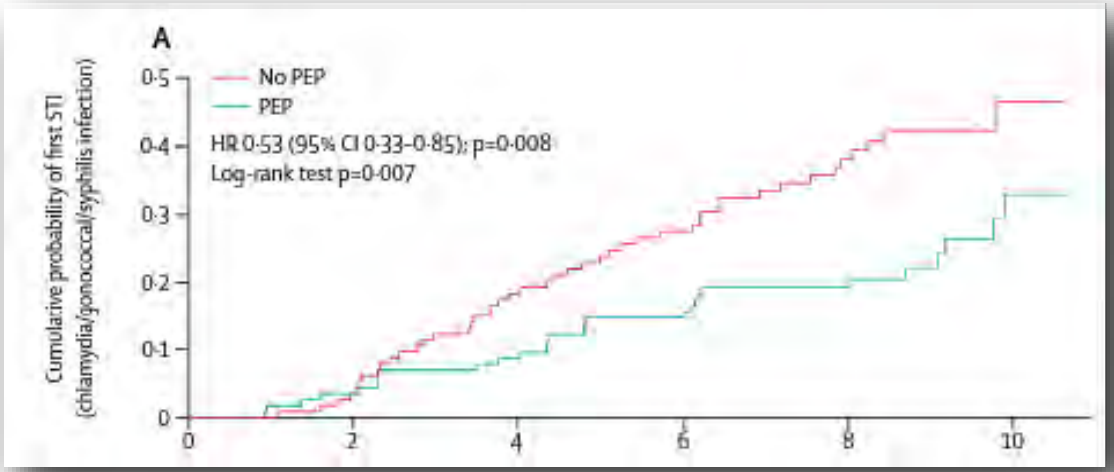
Methods All participants attending their scheduled visit in the open-label extension of the ANRS IPERGAY trial in France (men aged 18 years or older having condomless sex with men and using pre-exposure prophylaxis for HIV with tenofovir disoproxil fumarate plus emtricitabine) were eligible for inclusion 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.

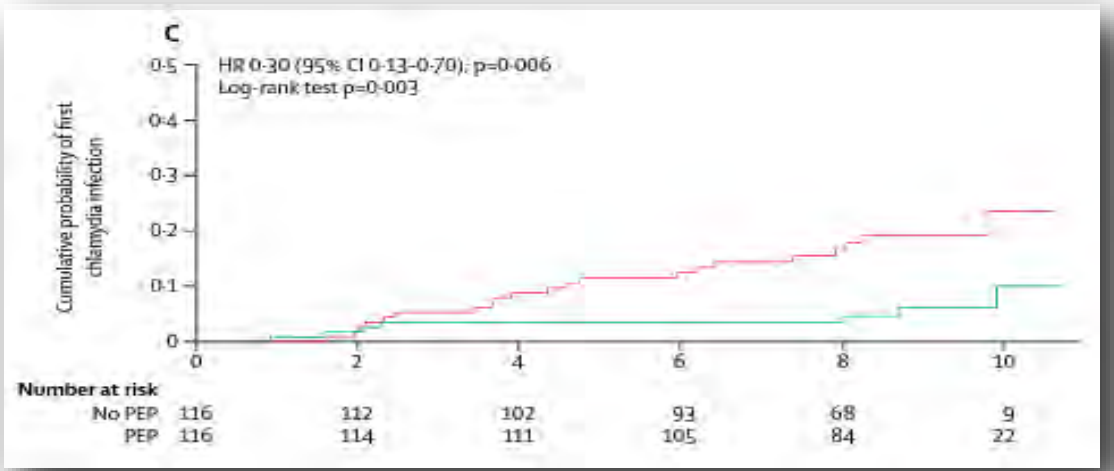
Findings Between July 20, 2015, and Jan 21, 2016, we randomly assigned 232 participants (n=116 in the doxycycline PEP group and n=116 in the no-PEP group) who were followed up for a median of 8·7 months (IQR 7·8–9·7). Participants in the PEP group used a median of 680 mg doxycycline per month (IQR 280–1450). 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

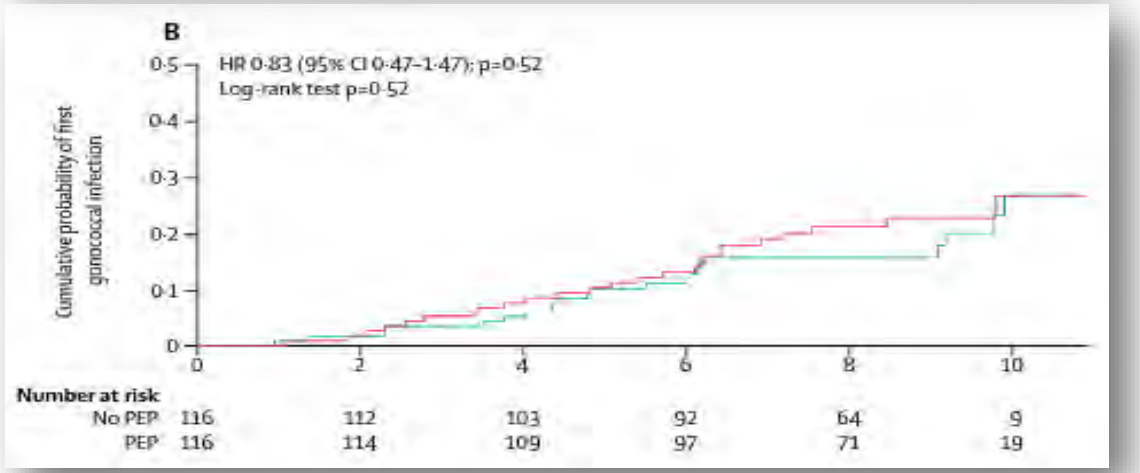
- **Design:** Multicenter, open-label, randomized, controlled, trial
- **Inclusion:**
  - MSM on PrEP (age >18)
  - Enrolled in ANRS IPERGAY Study
  - Condomless sex with men
- **Intervention**: 200 mg of doxycycline up to 72 hours after condomless sex

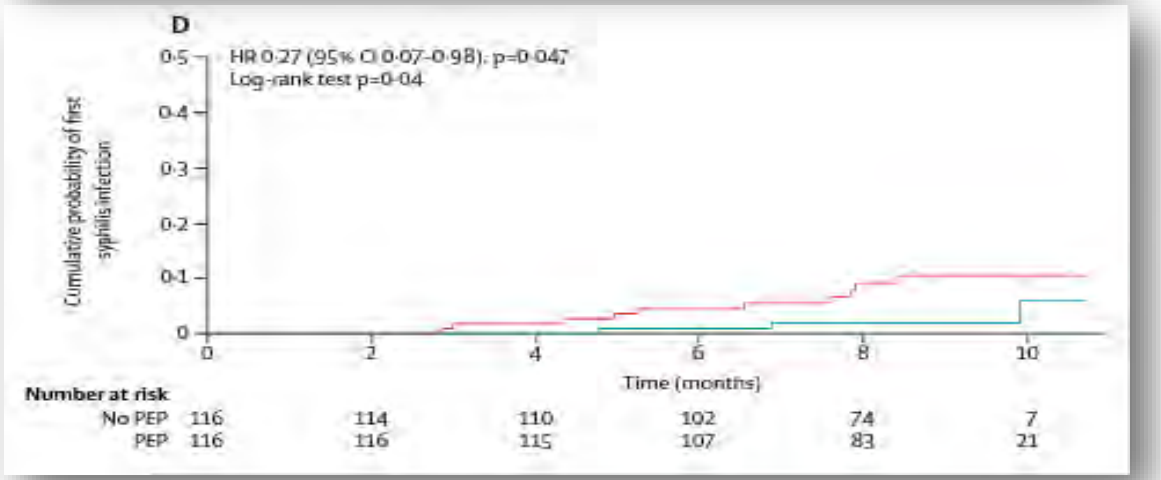
Molina JM, Charreau I, Chidiac C, et al. Post-exposure prophylaxis with doxycycline to prevent sexually transmitted infections in men who have sex with men: an open-label randomised substudy of the ANRS IPERGAY trial. Lancet Infect Dis. 2018;18(3):308-317. doi:10.1016/S1473-3099(17)30725-9

Doxy-PEP **Prevents** Chlamydia and Syphilis









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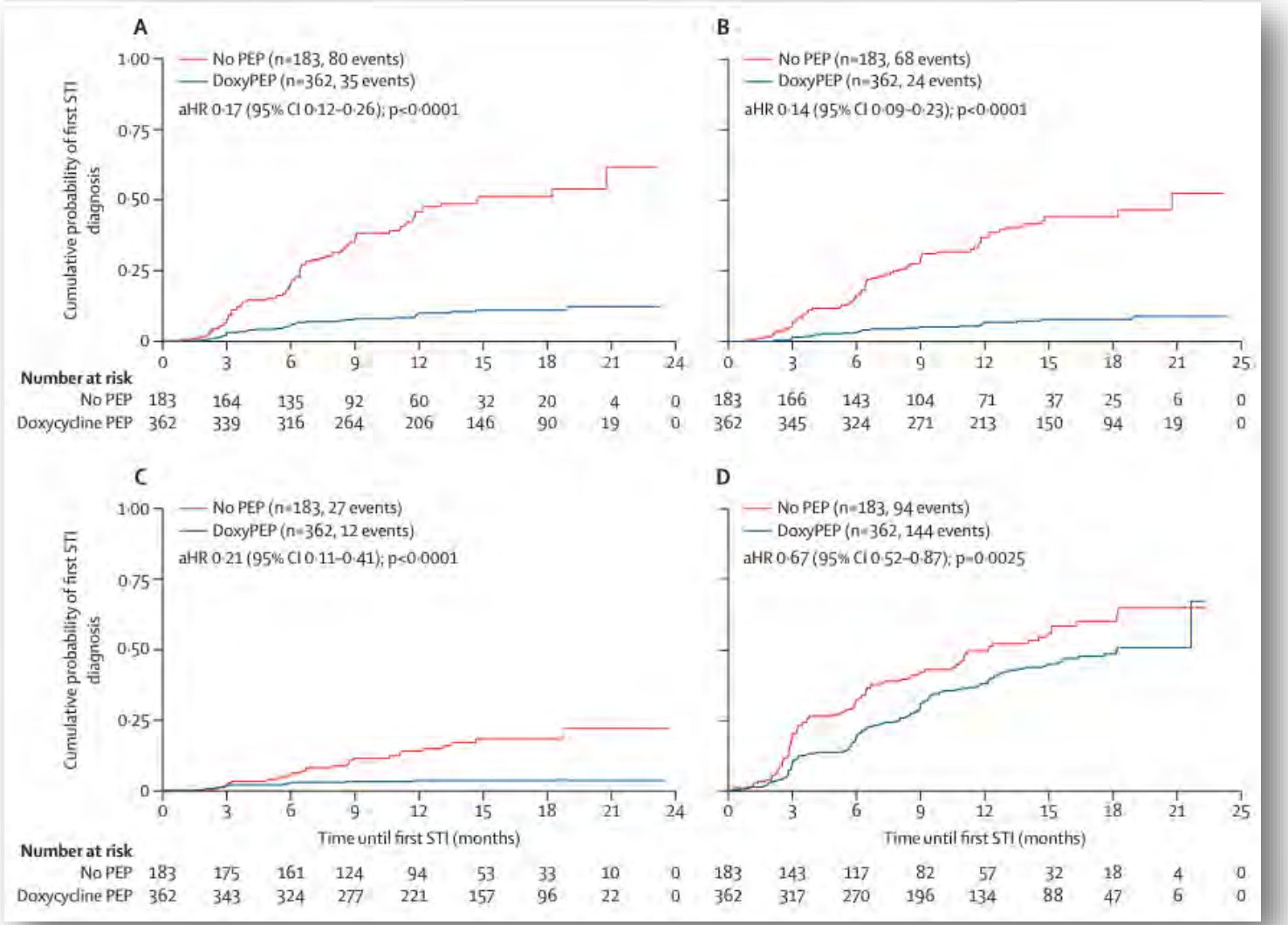
DoxyPEP **Prevents** STIs in DoxyVac



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dPEP Trial - Does Doxy-PEP Work in Women?

STUDY PROTOCOL Open Access

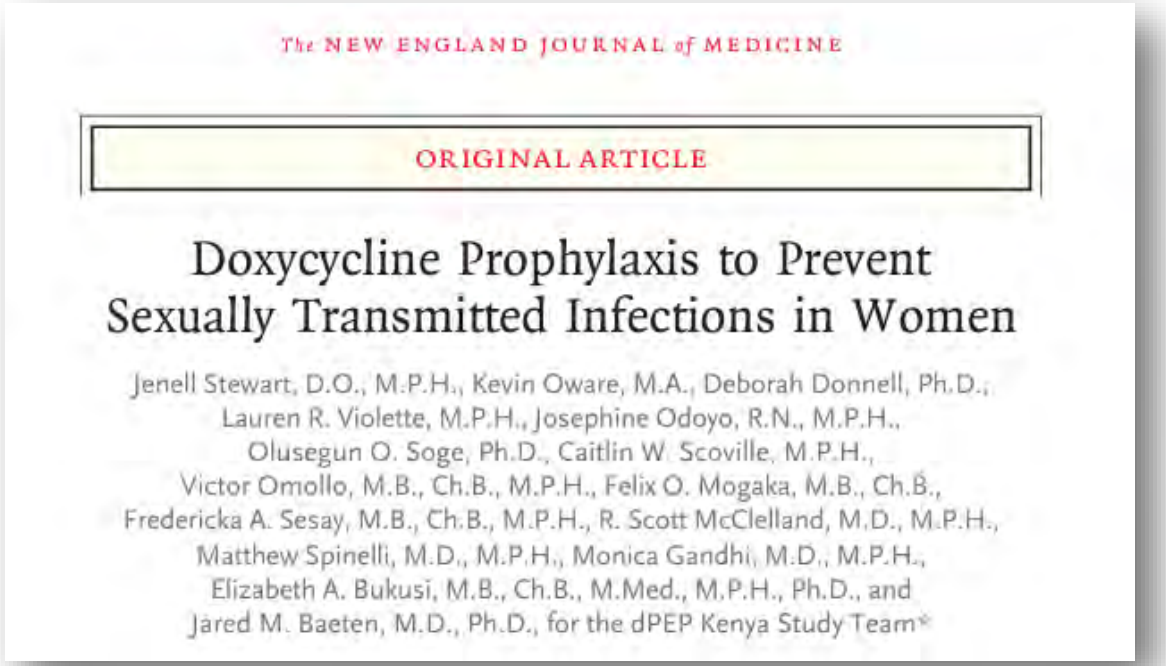
Doxycycline post-exposure prophylaxis for prevention of sexually transmitted infections among Kenyan women using HIV pre-exposure prophylaxis: study protocol for an open-label randomized trial

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



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

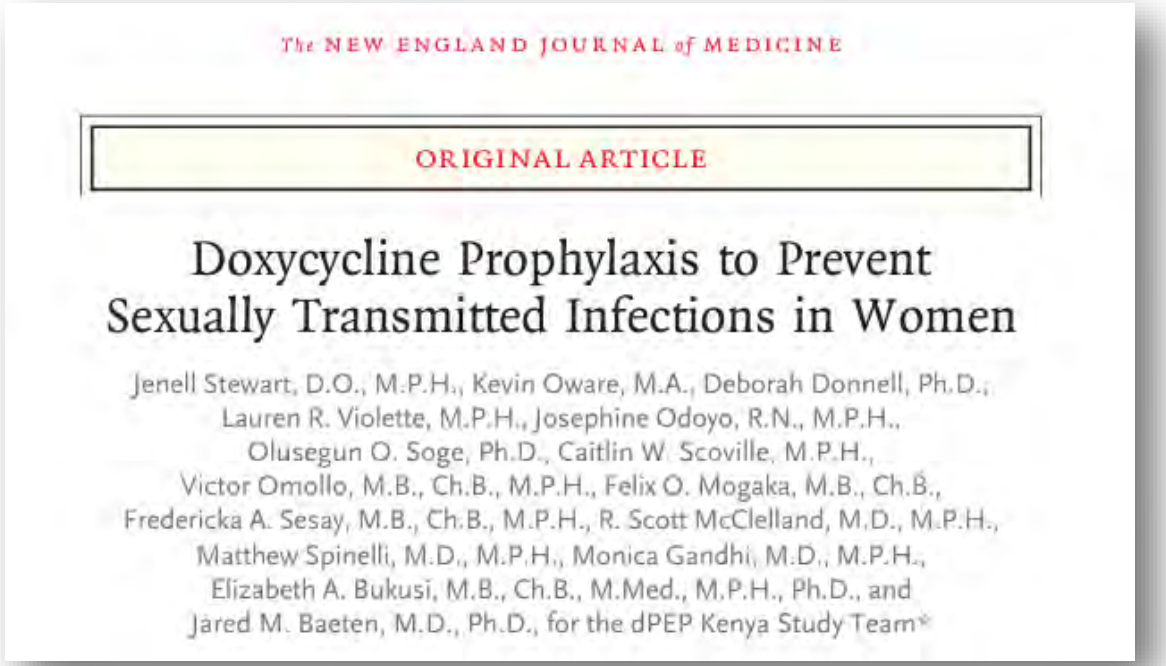
Doxycycline Prophylaxis to Prevent Sexually Transmitted Infections in Women

Jenell Stewart, D.O., M.P.H., Kevin Oware, M.A., Deborah Donnell, Ph.D., Lauren R. Violette, M.P.H., Josephine Odoyo, R.N., M.P.H., Olusegun O. Soge, Ph.D., Caitlin W. Scoville, M.P.H., Victor Omollo, M.B., Ch.B., M.P.H., Felix O. Mogaka, M.B., Ch.B., Fredericka A. Sesay, M.B., Ch.B., M.P.H., R. Scott McClelland, M.D., M.P.H., Matthew Spinelli, M.D., M.P.H., Monica Gandhi, M.D., M.P.H., Elizabeth A. Bukusi, M.B., Ch.B., M.Med., M.P.H., Ph.D., and Jared M. Baeten, M.D., Ph.D., for the dPEP Kenya Study Team*

- Overall STI incidence was 27 per 100 person-years
- 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
- Women assigned to doxy-PEP reported coverage of 78% of sex acts
- Among 50 randomly selected participants in the doxycycline-PEP group, doxycycline was detected in 58 of 200 hair samples (29.0%).

https://www.nejm.org/doi/full/10.1056/NEJMoa2304007

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



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

https://www.nejm.org/doi/full/10.1056/NEJMoa2304007

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
- **FoXXy Doxy** – ATN/HPTN trial in persons assigned female at birth

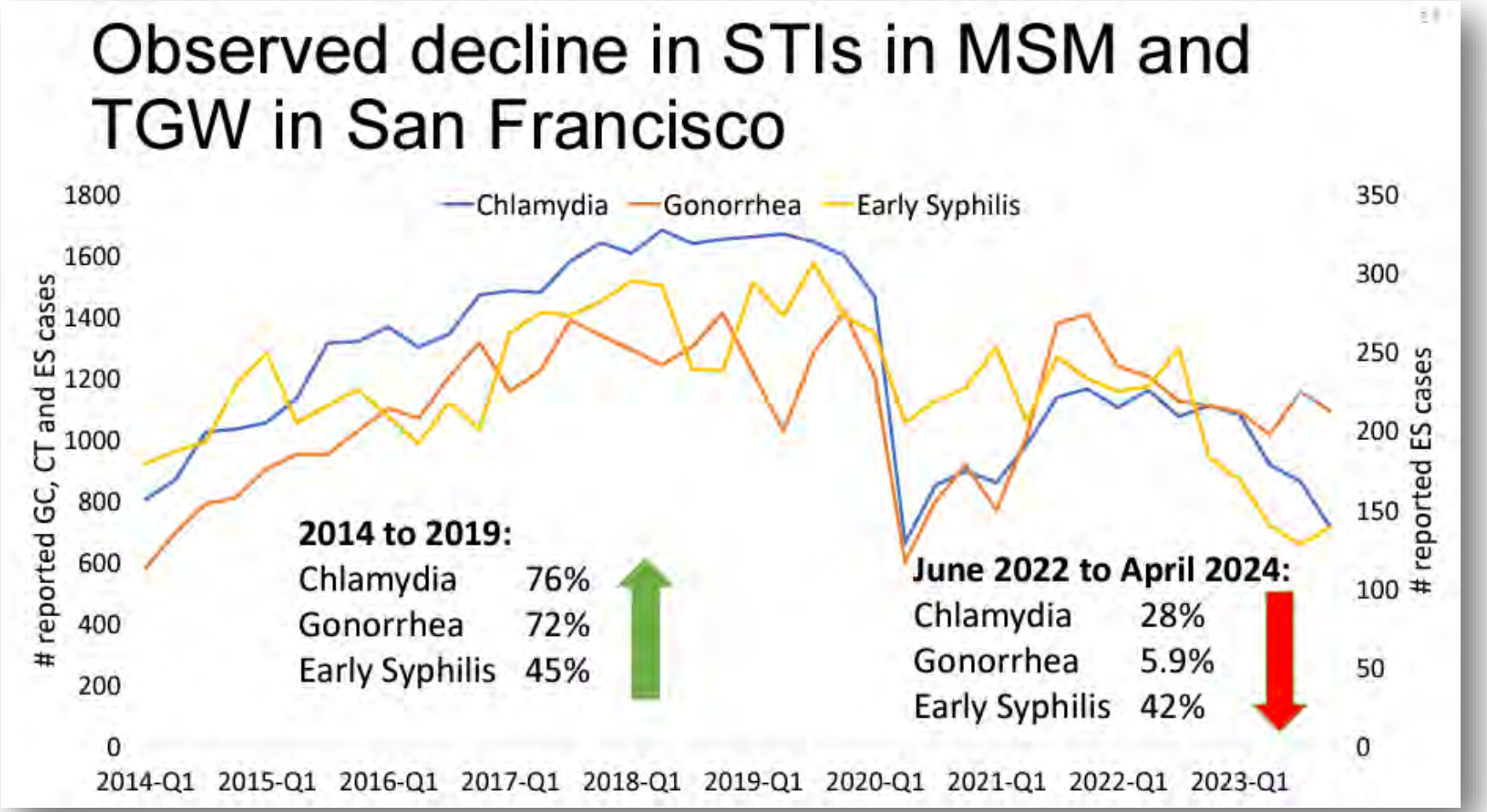
What We Know About Doxy-PEP From Trials

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

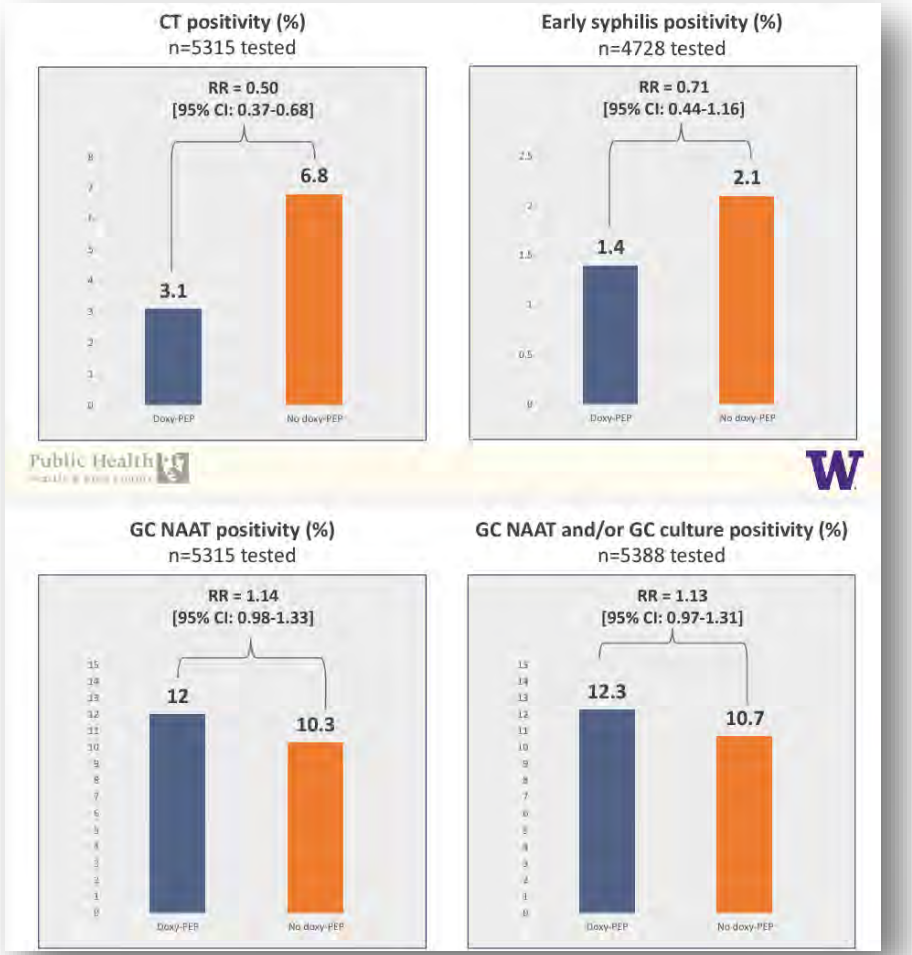
MSM = men who have sex with men, TGW = transgender women, PWH = Persons with HIV, CT = Chlamydia, GC = Gonorrhea, OR = odds ratio, HR = hazards ratio RR = Relative risk reduction () = Confidence intervals IQR() = Interquartile range

- 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

San Francisco



Seattle Washington (Kings County Sexual Health



- Presented at 2024 STI Prevention Conference

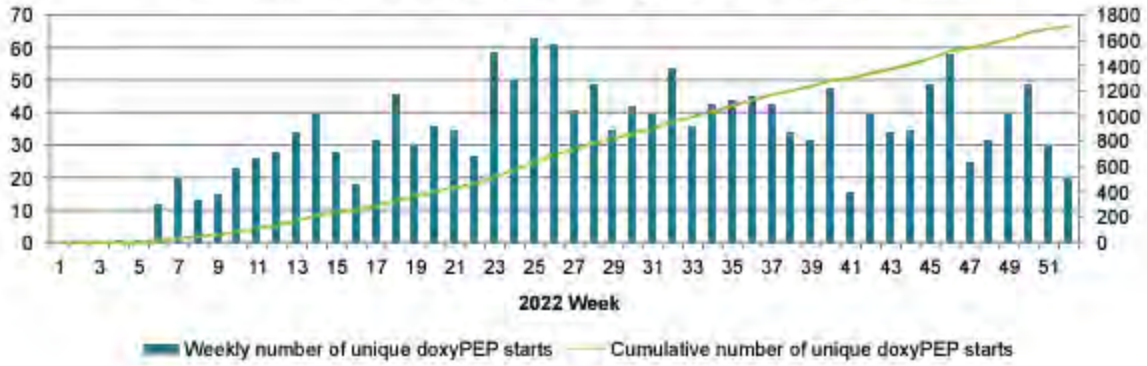
Boston (Fenway)

Results: DoxyPEP uptake

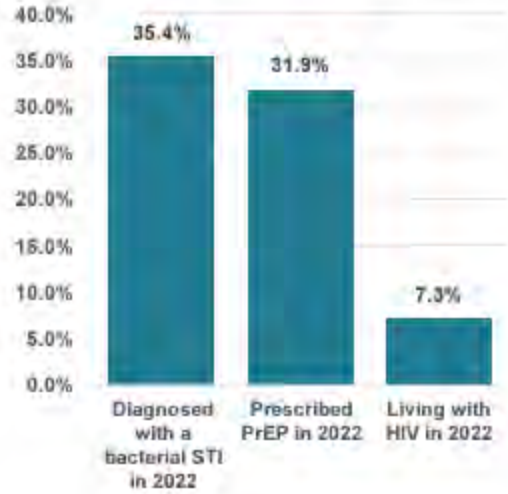
In 2023, 1,712 unique patients received doxyPEP

The highest weekly number of doxyPEP initiations was 63

Cumulative number of doxyPEP starts in 2023



DoxyPEP uptake among specific groups:

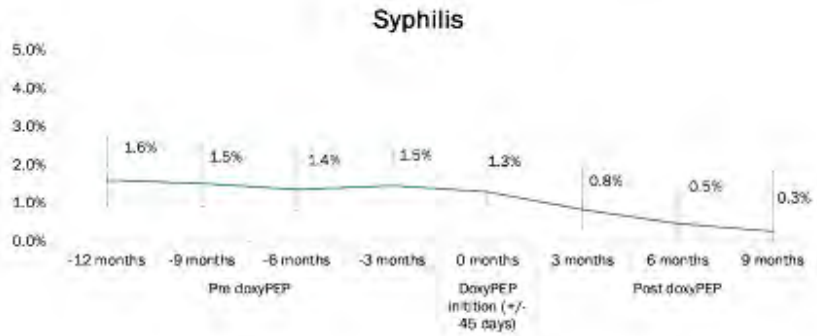


- Presented at 2024 STI Prevention Conference

Boston (Fenway)

STI positivity among doxyPEP users

Before and after starting doxyPEP

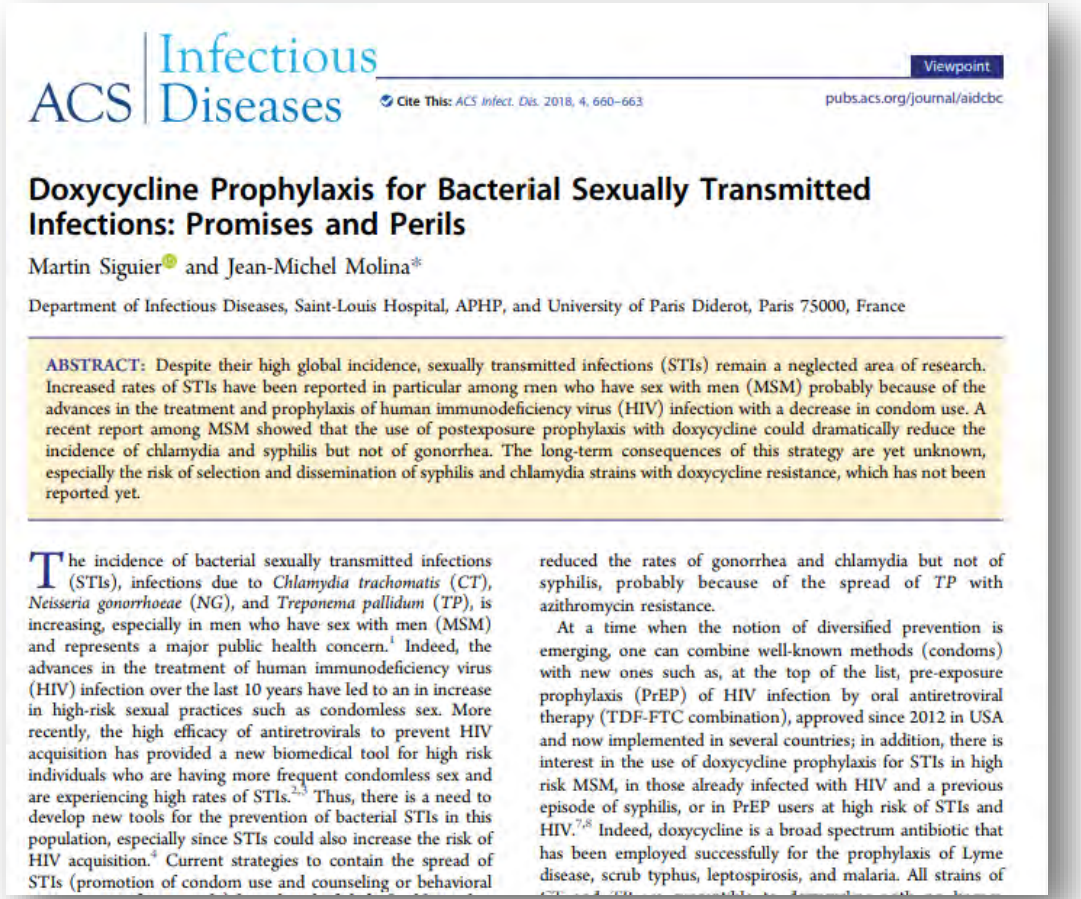


	Overall reduction from 12m pre-doxyPEP to 9m post-doxyPEP		
	Rate ratio (CI)	P-Value	Relative decline
Chlamydia	0.33 (0.25-0.44)	<0.001	66.8%
Gonorrhea	0.95 (0.78-1.15)	0.751	-
Syphilis	0.35 (0.12-0.71)	0.004	64.6%

- Presented at 2024 STI Prevention Conference

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

- 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?

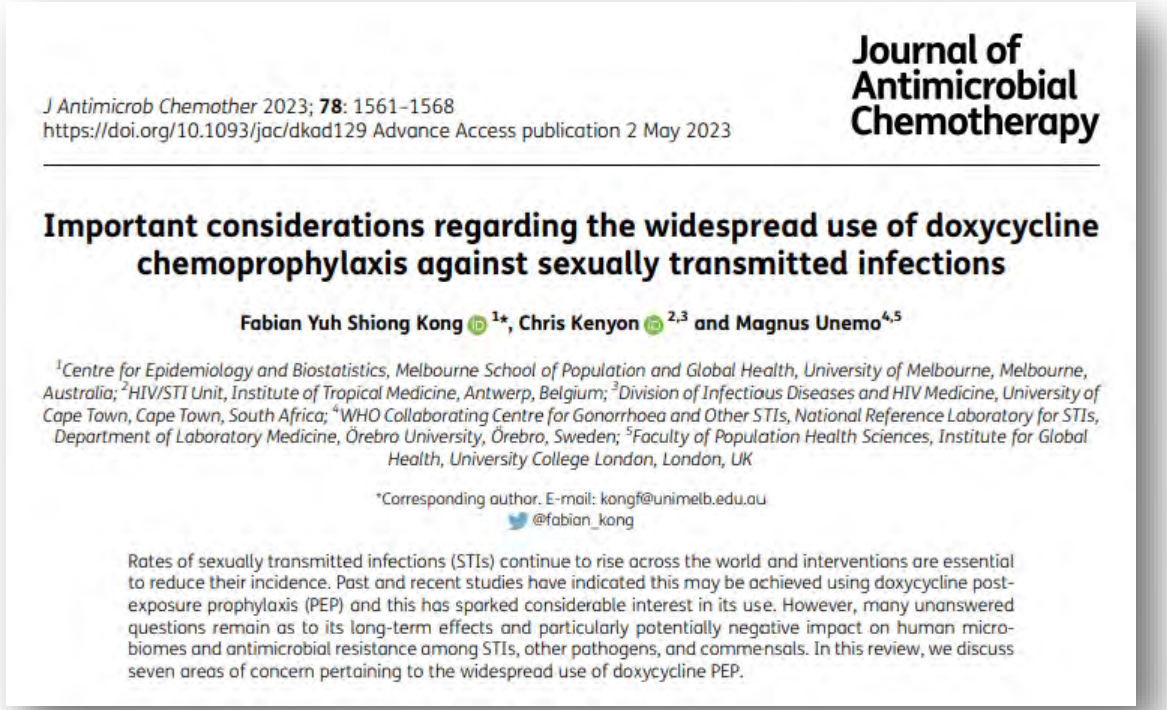
- DoxyPEP and DoxyVAC
  - No impact on sexual behavior
  - Changes in sexual behavior could impact Doxy-PEPs effectiveness

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]

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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

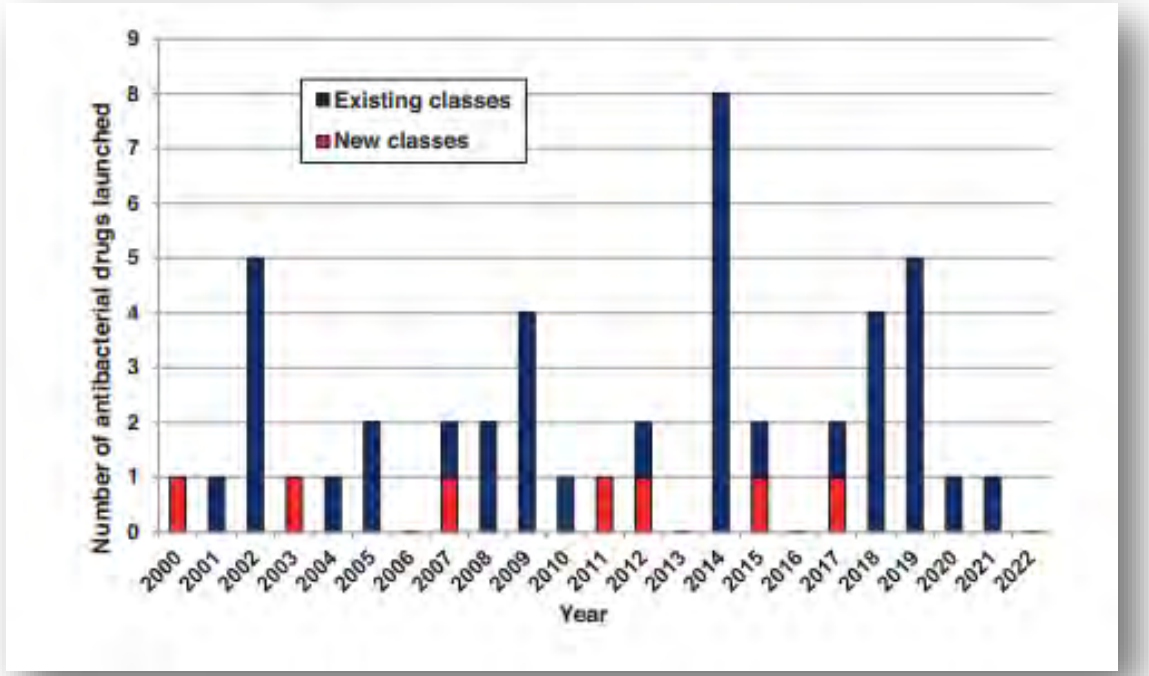
Antibiotics in the clinical pipeline as of December 2022

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

Antimicrobial Resistance

Chlamydia

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

Syphilis

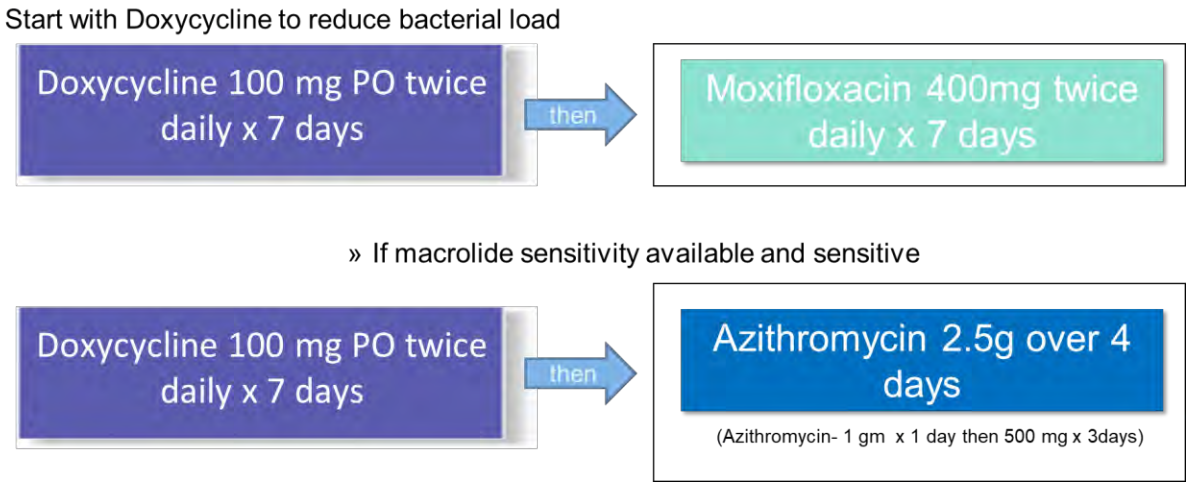
- No clinical resistance to tetracyclines in *Treponema pallidum*
- Widespread macrolide resistance was seen with a single-point mutation

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

- ***Mycoplasma genitalium***
  - Previously an "emerging" STI
  - Persistent urethritis in men and women
  - Test using first-void urine or urethral swab, send for NAAT
  - Treatment based on testing availability



- Intrinsically <u>resistant</u> to:
  - Cell wall and folic acid inhibitors
- High <u>resistance</u> 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

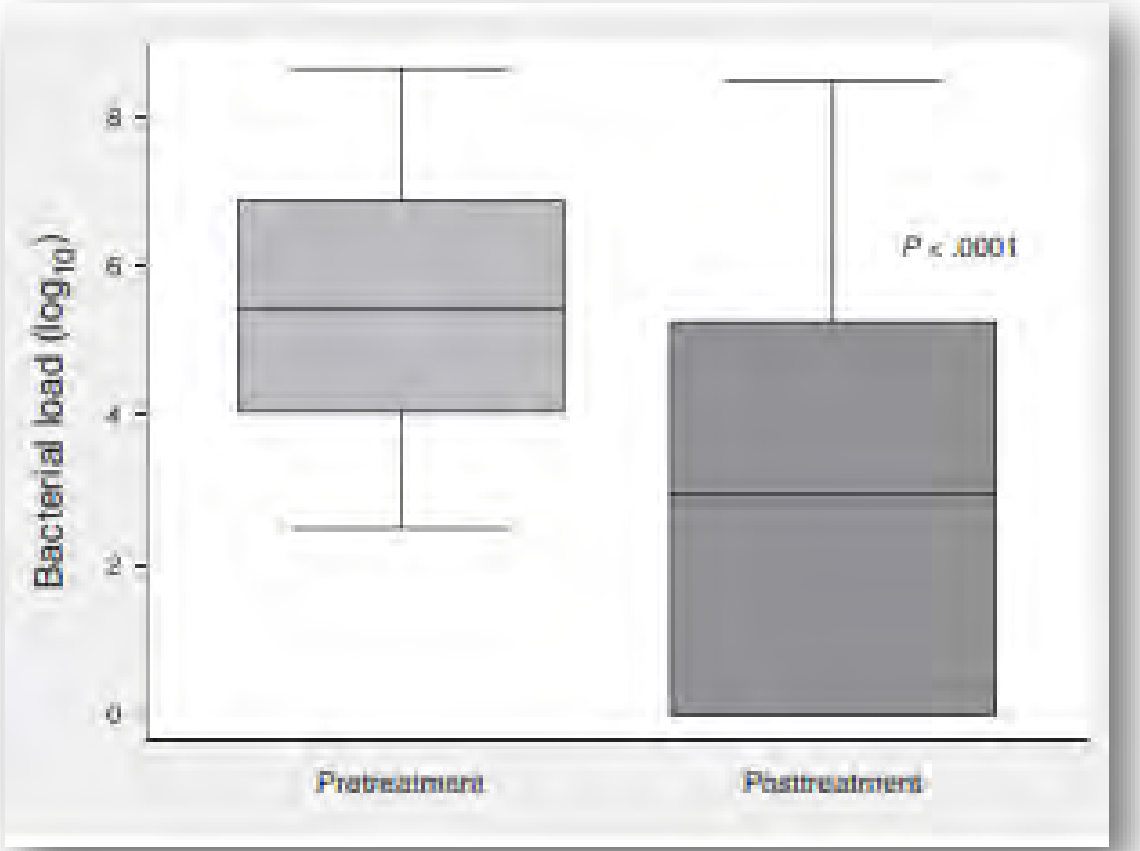
Tim R. H. Read,[1,2] Christopher K. Fairley,[1,2] Gerald L. Murray,[3,4,5,6] Jorgen S. Jensen,[7] Jennifer Danielewski,[3,4] Karen Worthington,[2] Michelle Doyle,[2] Elisa Mokany,[8] Litty Tan,[8] Eric P. F. Chow,[1,2] Suzanne M. Garland,[3,4,6,9] and Catriona S. Bradshaw[1,2]

[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.)

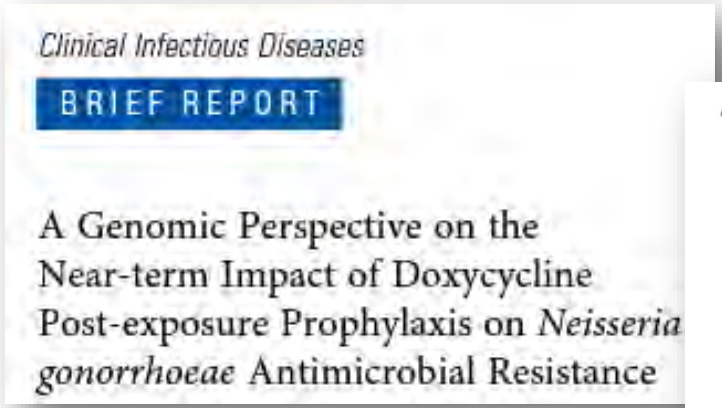
Background. Rising macrolide and quinolone resistance in *Mycoplasma genitalium* necessitate new treatment approaches. We evaluated outcomes of sequential antimicrobial therapy for *M. genitalium* guided by a macrolide-resistance assay.

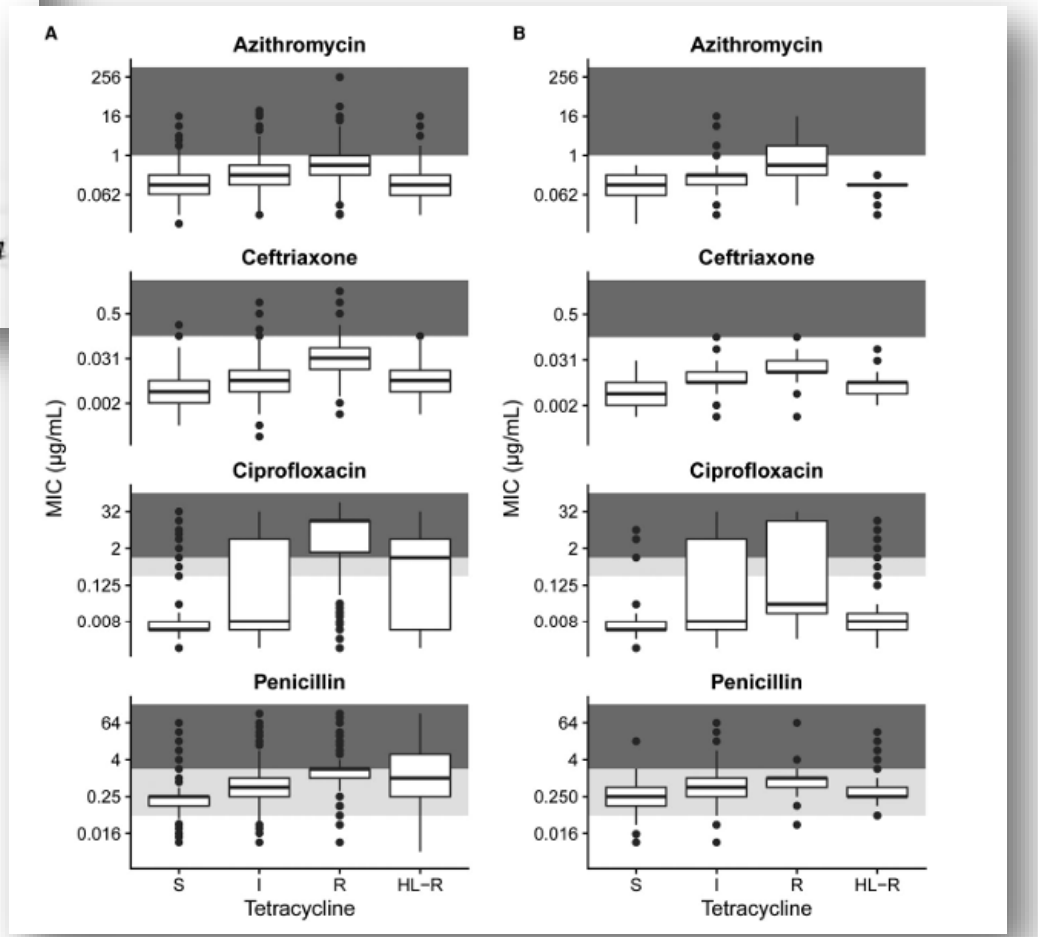
Methods. In mid-2016, Melbourne Sexual Health Centre switched from azithromycin to doxycycline (100 mg twice daily for 7 days) for nongonococcal urethritis, cervicitis, and proctitis. Cases were tested for *M. genitalium* and macrolide-resistance mutations (MRMs) by polymerase chain reaction. Directly 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

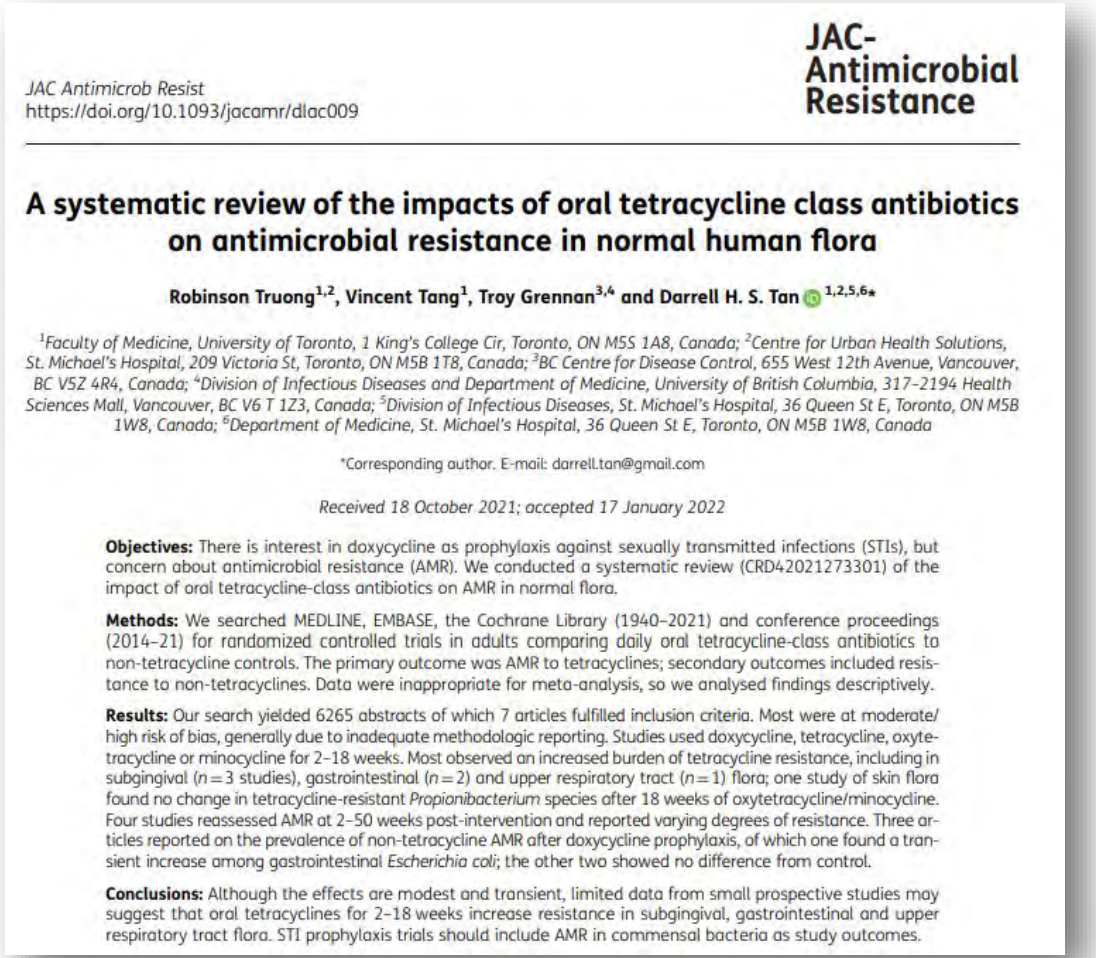




- Risk of **resistance to tetracyclines** (doxycycline) in gonorrhea
- Risk of **cross resistance** to other antimicrobials including beta-lactams like Ceftriaxone

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

Received 18 October 2021; accepted 17 January 2022

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.

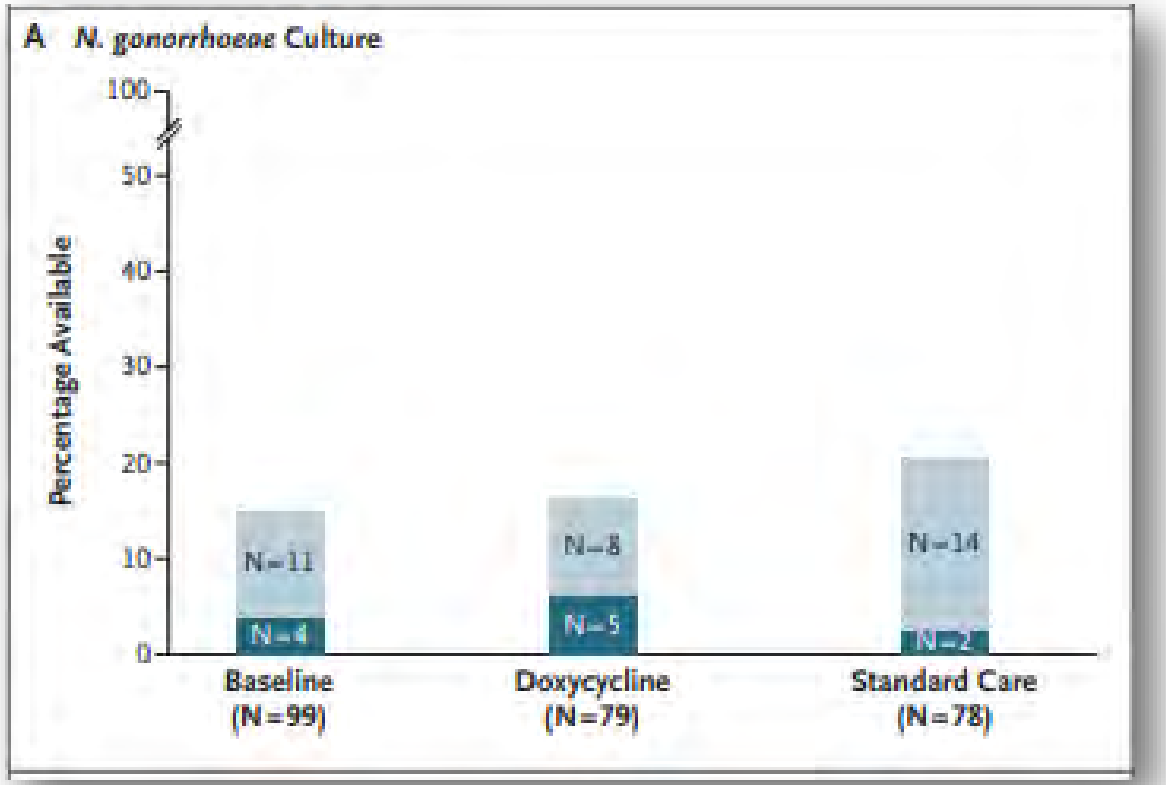
Results: Our search yielded 6265 abstracts of which 7 articles fulfilled inclusion criteria. Most were at moderate/high risk of bias, generally due to inadequate methodologic reporting. Studies used doxycycline, tetracycline, oxytetracycline or minocycline for 2–18 weeks. Most observed an increased burden 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.

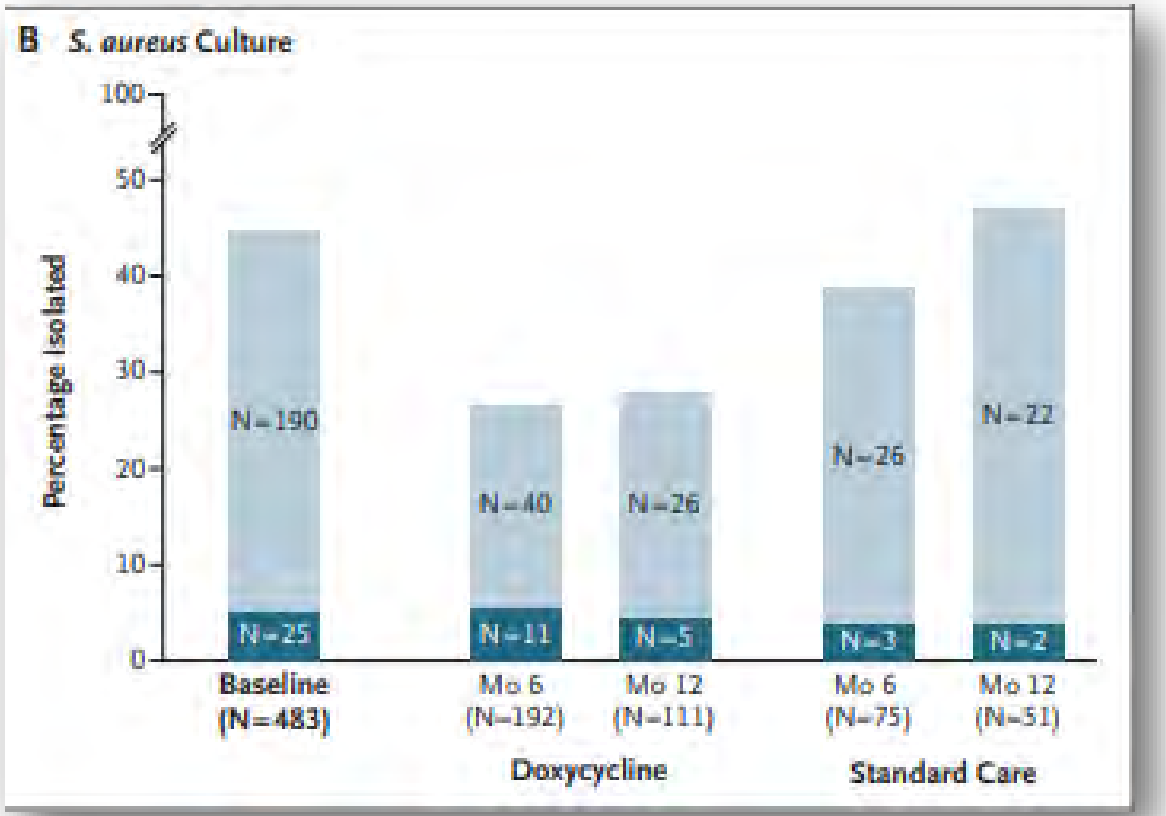
Conclusions: Although the effects are modest and transient, limited data from small prospective studies may suggest that oral tetracyclines for 2–18 weeks increase resistance in subgingival, gastrointestinal and upper respiratory tract flora. STI prophylaxis trials should include AMR in commensal bacteria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

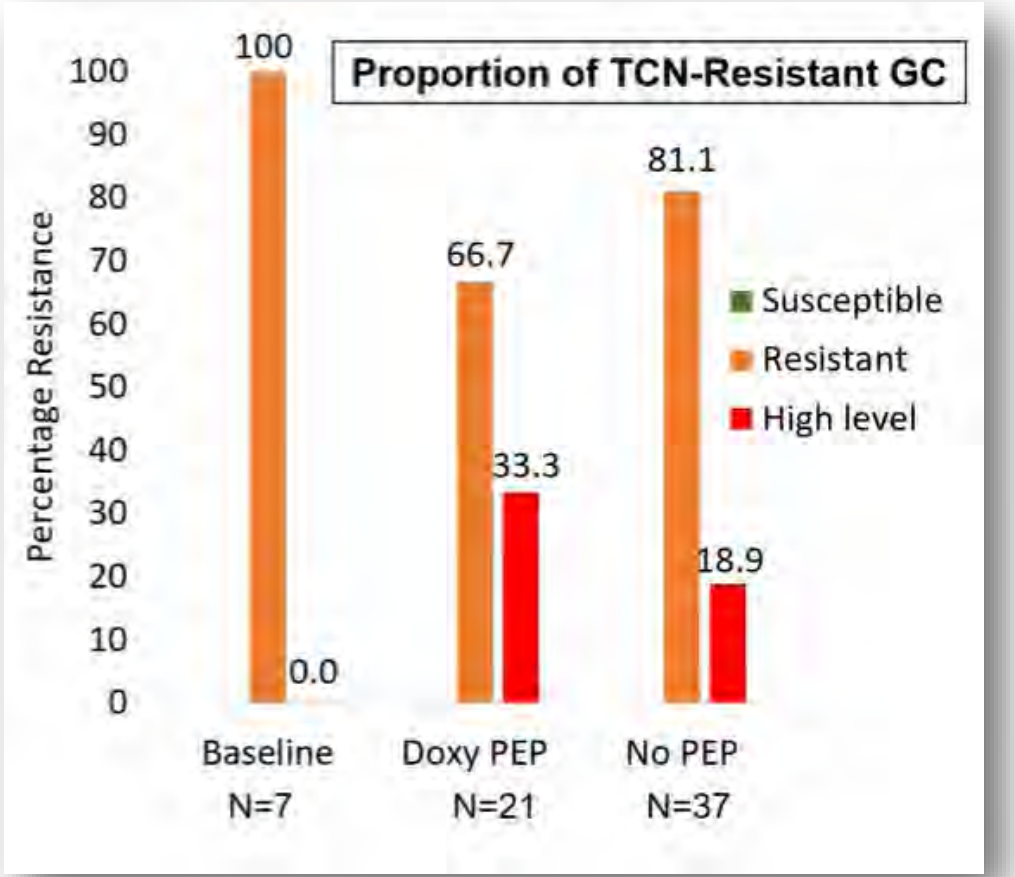
Antimicrobial Resistance – DoxyPEP Study

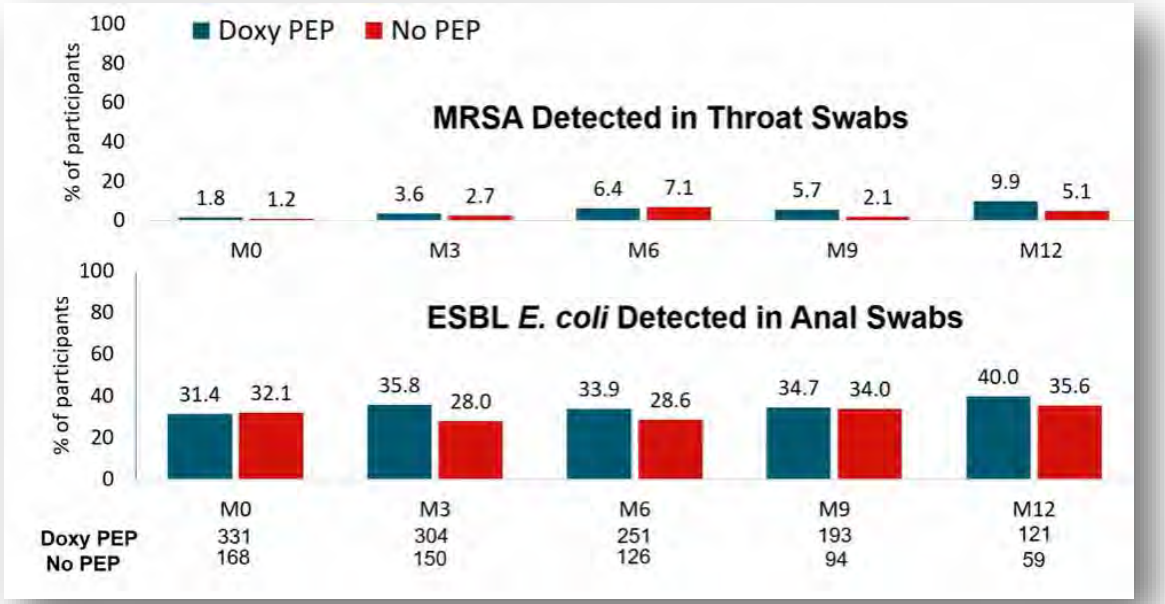




- Luetkemeyer AF, Donnell D, Dombrowski JC, et al. Postexposure Doxycycline to Prevent Bacterial Sexually Transmitted Infections. N Engl J Med. 2023;388(14):1296-1306. doi:10.1056/NEJMoa2211934

Antimicrobial Resistance – DoxyVac Study





- 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.

Doxy-PEP Harms Summary

Well known side effects:

- Gastrointestinal distress
- Photosensitivity
- Pill esophagitis

Growing understanding:

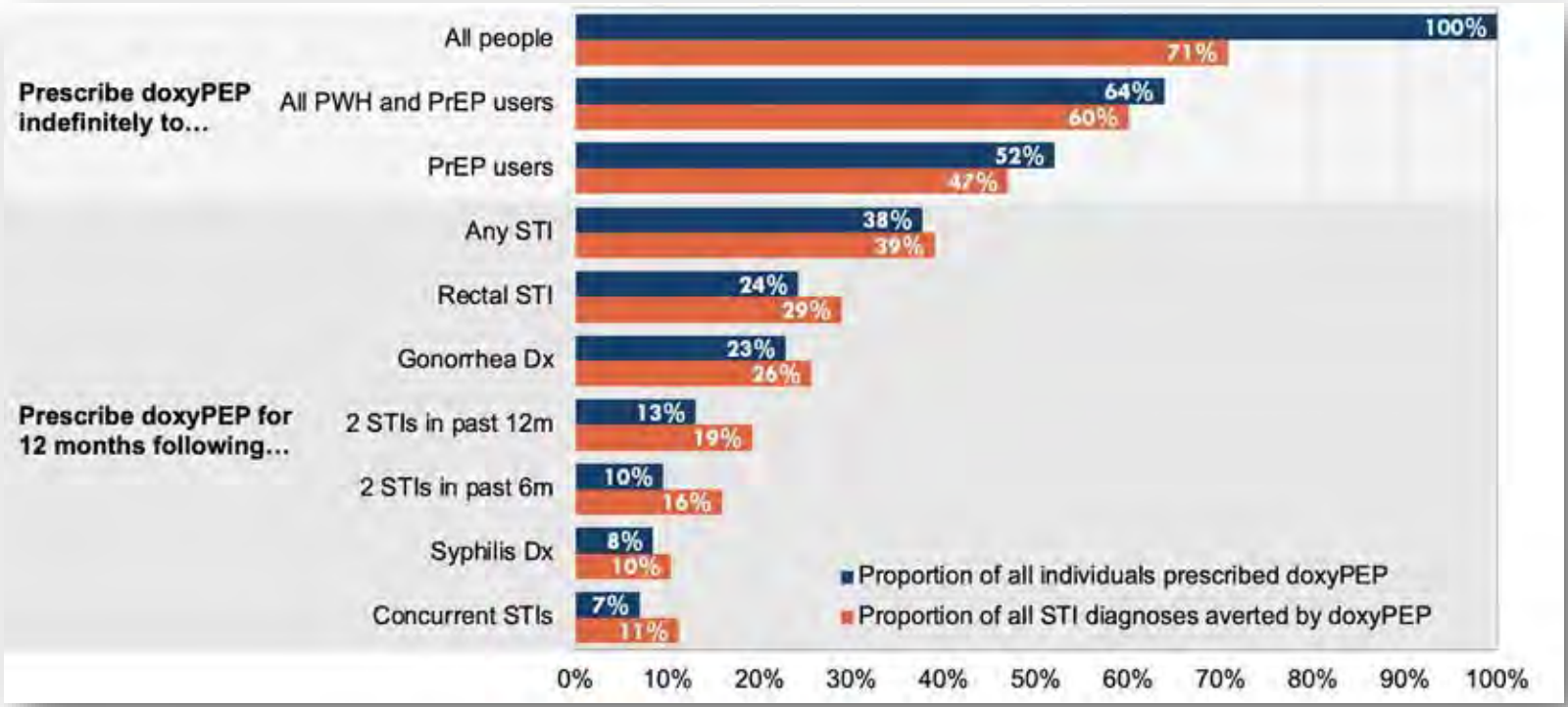
- No resistance seen with chlamydia and syphilis
- Decreased colonization with S. Aureus but increased GAS
- Growing resistance to Doxycycline in STIs (GC) and commensals (S. Aureus)

Unknowns:

- Impact on M. Gen
- Impact on the microbiome
- Impact on STI presentations
- Cross-resistance with other antibiotics

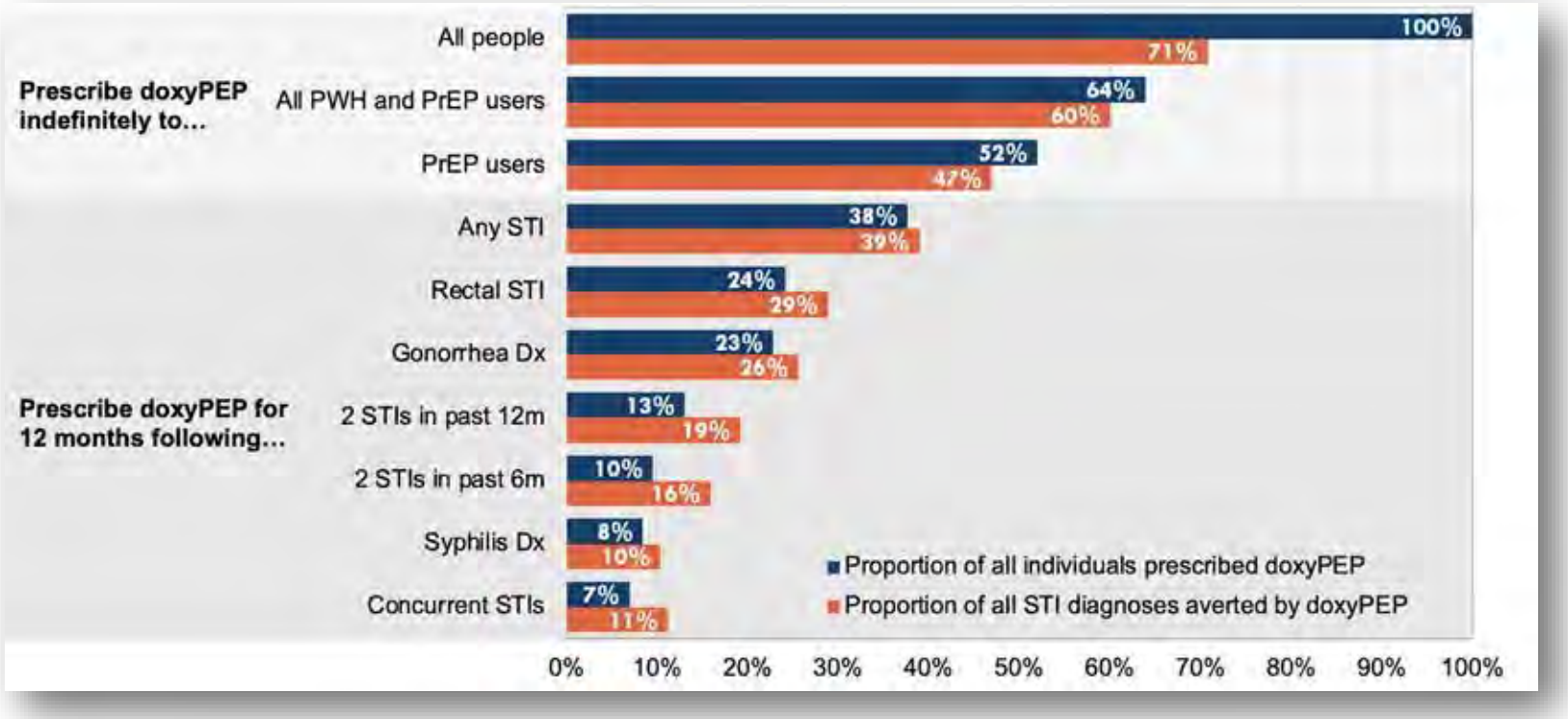
Implementation Questions

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



- 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

Who should be given DoxyPEP?



The most **efficient** prescribing strategies were **based on STI history** rather than HIV status or PrEP use.

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

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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Lancet Microbe 2023
Published Online October 23, 2023
https://doi.org/10.1016/S2666-5247(23)00314-2

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

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://www.bashh.org/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.[9–11]

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[2–5] — 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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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

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….
- 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.**
- 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

Eligibility - CDC Guidelines

CDC Clinical Guidelines on the Use of Doxycycline Postexposure Prophylaxis for Bacterial Sexually Transmitted Infection Prevention, United States, 2024

Recommendation*	Strength of recommendation and quality of evidence†
• Providers should counsel all gay, bisexual, and other men who have sex with men (MSM) and transgender women (TGW) with a history of at least one bacterial sexually transmitted infection (STI) (specifically, syphilis, chlamydia or gonorrhea) during the past 12 months about the benefits and harms of using doxycycline (any formulation) 200 mg once within 72 hours (not to exceed 200 mg per 24 hours) of oral, vaginal, or anal sex and should offer doxycycline postexposure prophylaxis (doxy PEP) through shared decision-making. Ongoing need for doxy PEP should be assessed every 3–6 months.	AI High-quality evidence supports this strong recommendation to counsel MSM and TGW and offer doxy PEP.
• No recommendation can be given at this time on the use of doxy PEP for cisgender women, cisgender heterosexual men, transgender men, and other queer and nonbinary persons.	Evidence is insufficient to assess the balance of benefits and harms of the use of doxy PEP

*Although not directly assessed in the trials included in these guidelines, doxy PEP could be discussed with MSM and TGW who have not had a bacterial STI diagnosed during the previous year but will be participating in sexual activities that are known to increase likelihood of exposure to STIs.
† See Table.

- https://www.cdc.gov/mmwr/volumes/73/rr/rr7302a1.htm

Testing Intervals

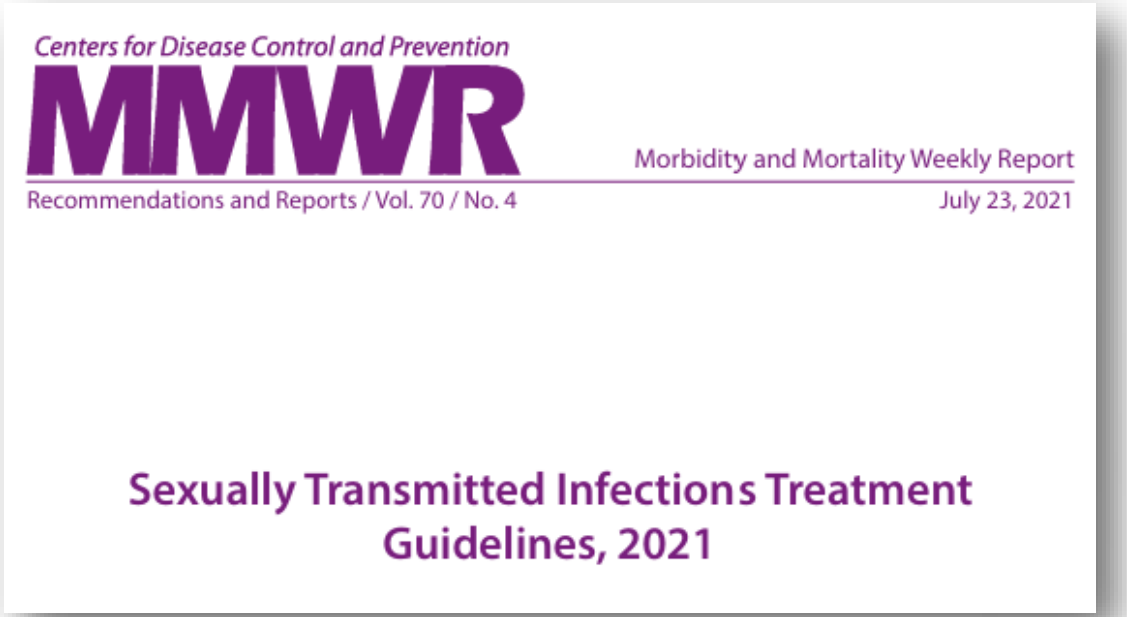
- Who should be given DoxyPEP?
- **What is the proper interval for STI testing for individuals on Doxy-PEP?**
- How does Doxy-PEP Impact STI Treatment?

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

STI Treatment

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



Exception

- ***Consider in-person exam, testing, and deferring empiric treatment for "exposure"***

• 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

How Do I Provide Doxy-PEP?

Eligibility - CDC Guidelines

CDC Clinical Guidelines on the Use of Doxycycline Postexposure Prophylaxis for Bacterial Sexually Transmitted Infection Prevention, United States, 2024

Recommendation*	Strength of recommendation and quality of evidence†
• Providers should counsel all gay, bisexual, and other men who have sex with men (MSM) and transgender women (TGW) with a history of at least one bacterial sexually transmitted infection (STI) (specifically, syphilis, chlamydia or gonorrhea) during the past 12 months about the benefits and harms of using doxycycline (any formulation) 200 mg once within 72 hours (not to exceed 200 mg per 24 hours) of oral, vaginal, or anal sex and should offer doxycycline postexposure prophylaxis (doxy PEP) through shared decision-making. Ongoing need for doxy PEP should be assessed every 3–6 months.	AI High-quality evidence supports this strong recommendation to counsel MSM and TGW and offer doxy PEP.
• No recommendation can be given at this time on the use of doxy PEP for cisgender women, cisgender heterosexual men, transgender men, and other queer and nonbinary persons.	Evidence is insufficient to assess the balance of benefits and harms of the use of doxy PEP

*Although not directly assessed in the trials included in these guidelines, doxy PEP could be discussed with MSM and TGW who have not had a bacterial STI diagnosed during the previous year but will be participating in sexual activities that are known to increase likelihood of exposure to STIs.
† See Table.

Initial Visit

- Screen for sexually transmitted infections (STIs) as indicated:
  - HIV Testing
  - Gonorrhea/Chlamydia NAAT testing (including extra-genital)
  - Syphilis testing
  - Hepatitis testing
  - Vaccination status
  - Counsel on
    - Prevention strategies
    - Risks and harms of Doxy-PEP
      - As well as using it for it's intended purpose
    - Drug-drug interactions (antacids, cations)

Doxy-PEP Harms

Well known side effects:

- Gastrointestinal distress
- Photosensitivity
- Pill esophagitis

Growing understanding:

- Decreased colonization with S. Aureus but increased GAS
- Growing resistance to Doxycycline in STIs (GC) and commensals (S. Aureus)

Unknowns:

- Impact on the microbiome
- Impact on STI presentations
- Cross-resistance with other antibiotics

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

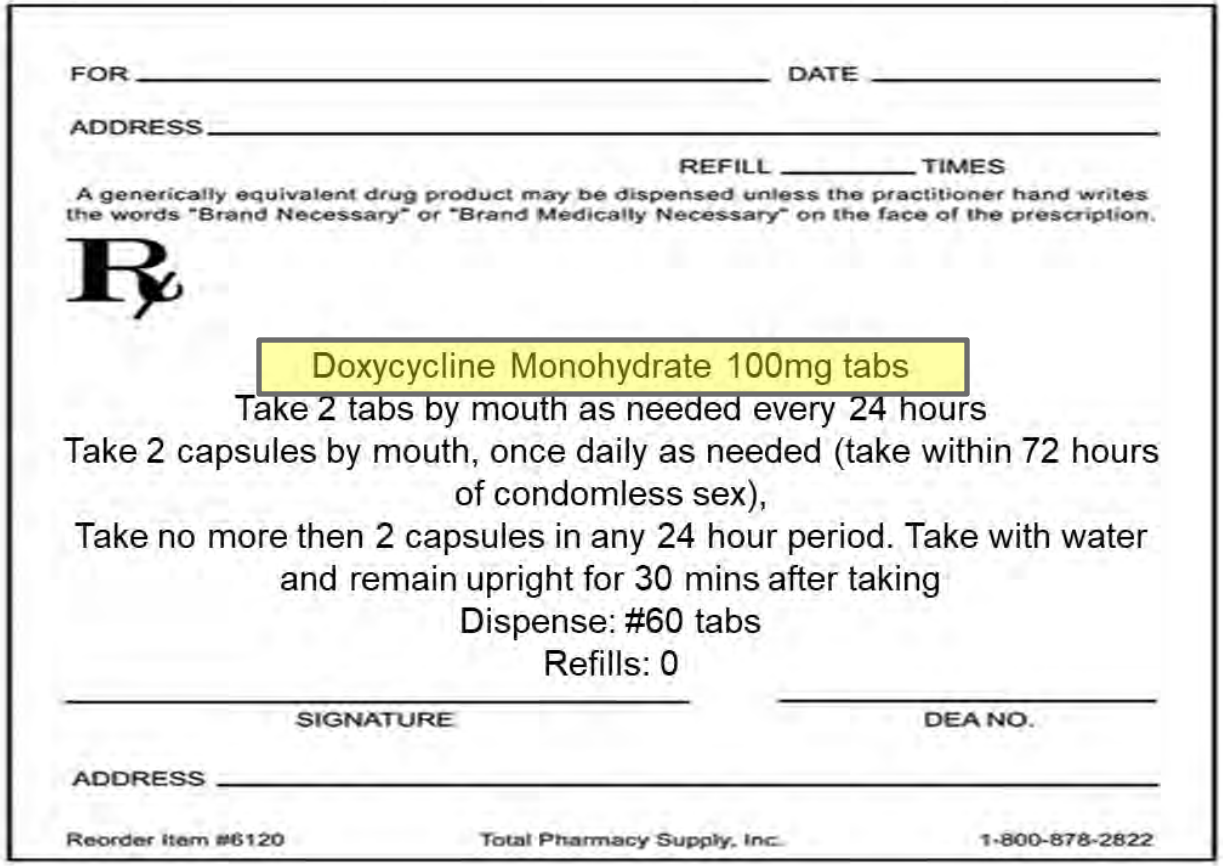
_____ _____

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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Refills: 0

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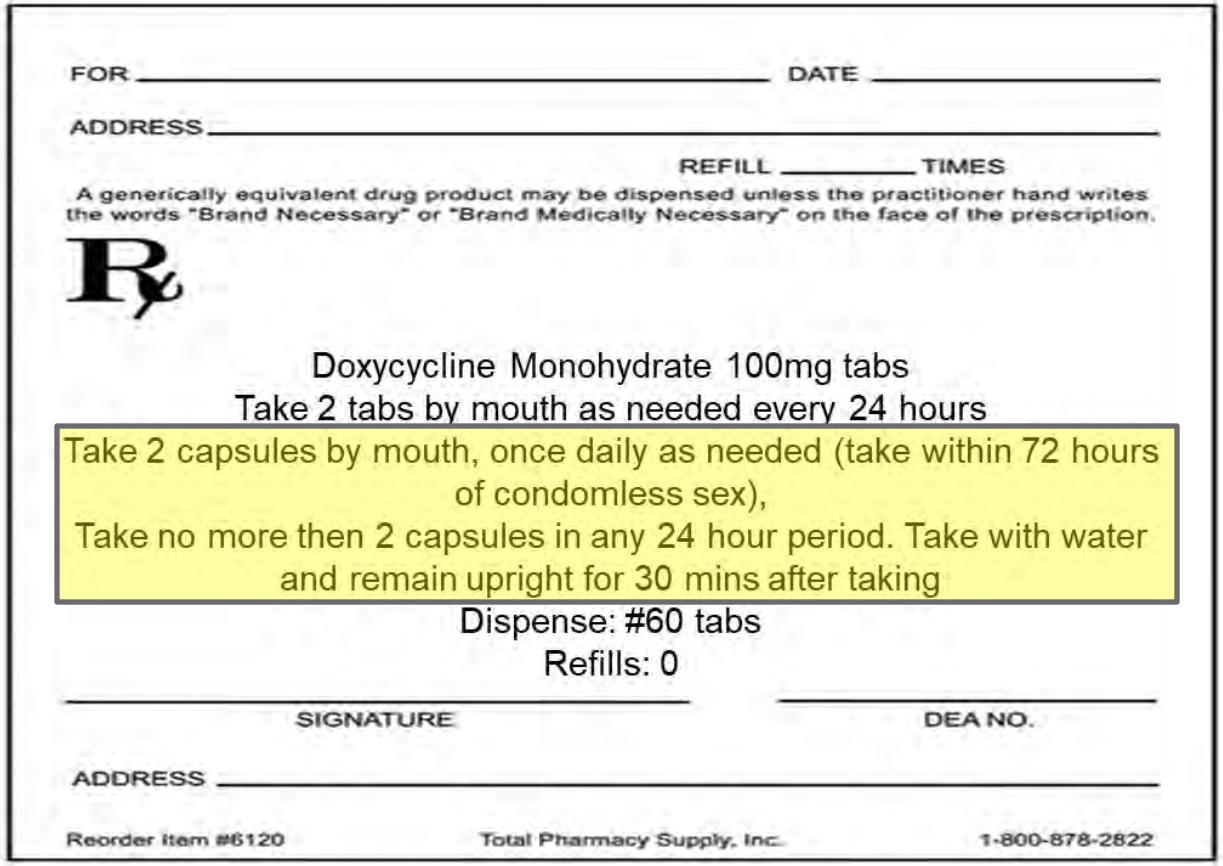
Hyclate or Monohydrate

- Hyclate – cheaper
- Monohydrate – less GI distress

How Do I Prescribe Doxy-PEP?



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Refills: 0

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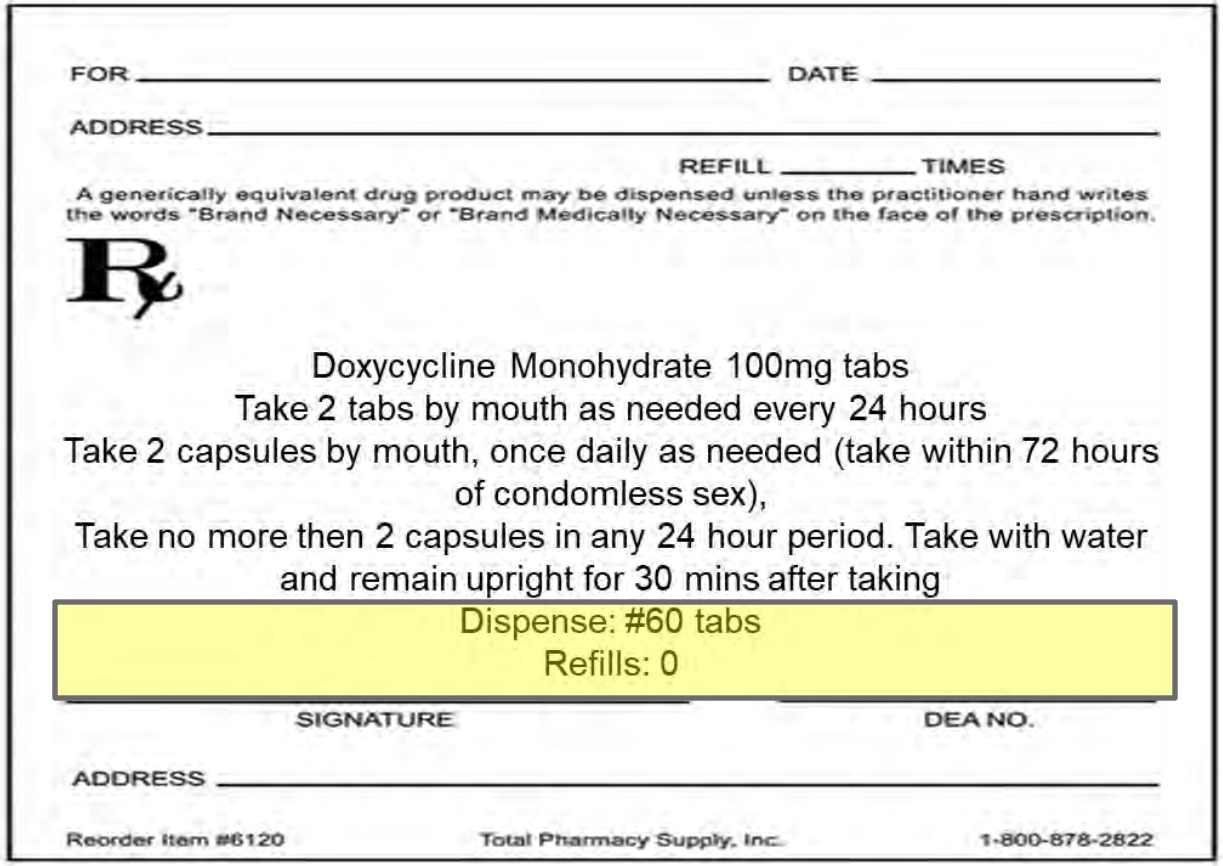
- Detailed instructions

How Do I Prescribe Doxy-PEP?



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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

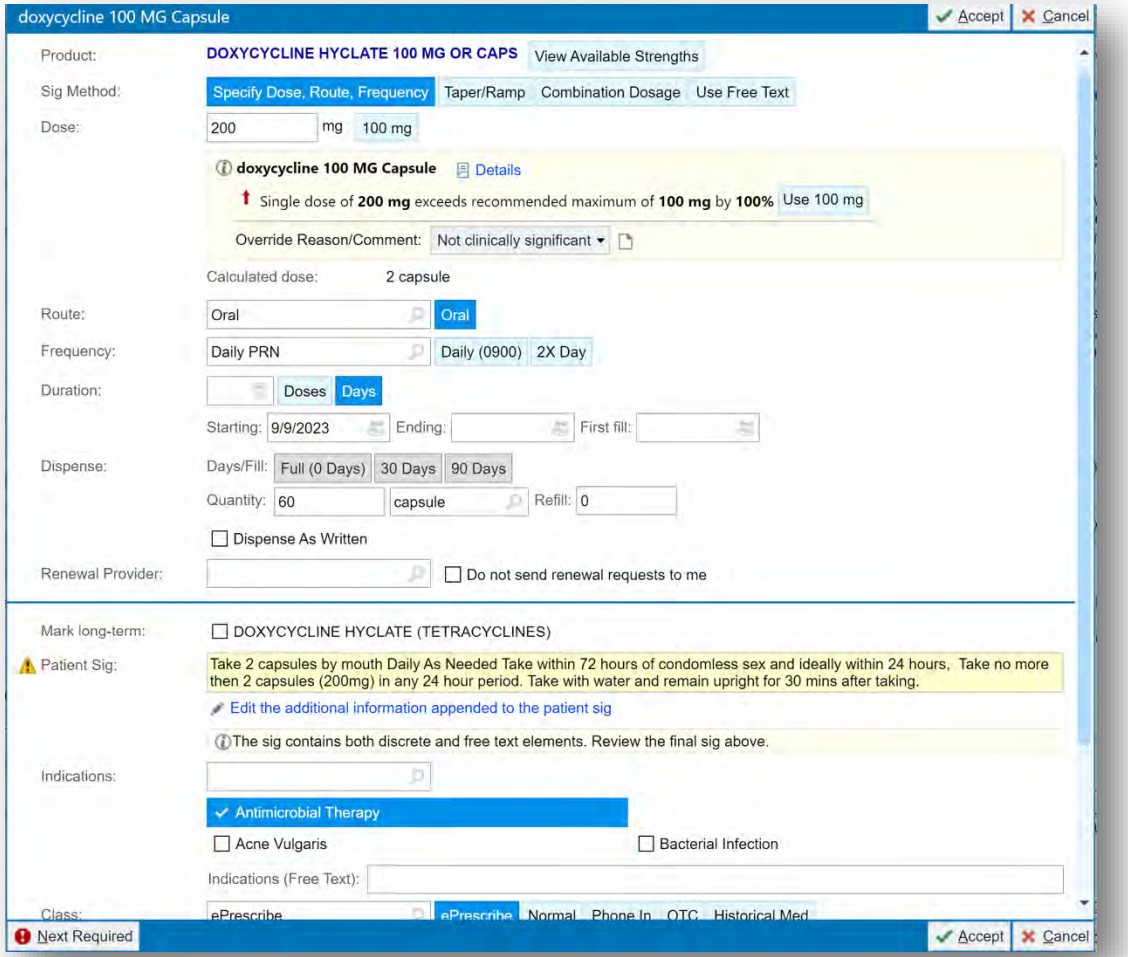
SIGNATURE DEA NO.

ADDRESS _____

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

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

How Do I Prescribe Doxy-PEP?



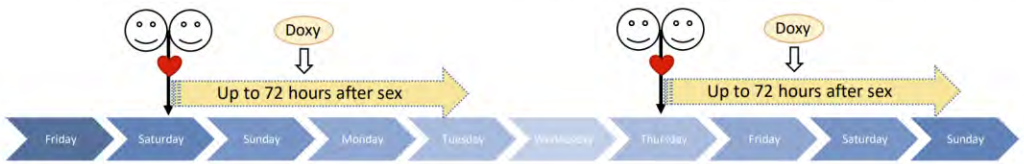
Patient Decision Aids

Doxy PEP – How to Take

= sex without a condom, including oral sex

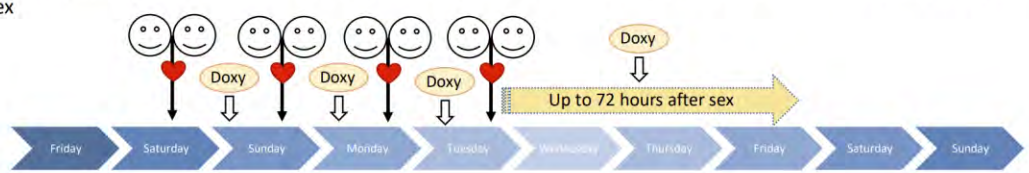
Two 100 mg pills of doxycycline ideally within 24 hours but no later than 72 hours after condomless oral, anal or vaginal sex

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.

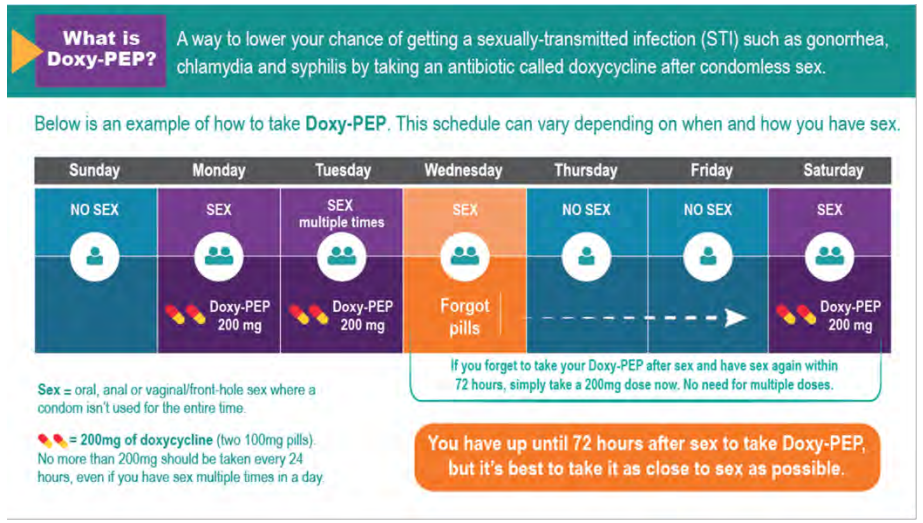
What are we still learning about doxy-PEP?

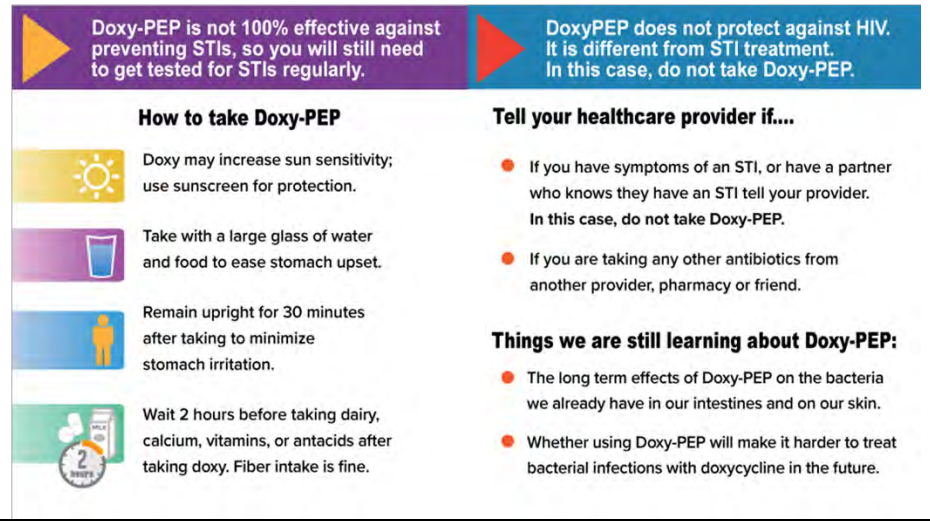
- Does it affect normal ("good") bacteria in our intestines?
- Could it increase or decrease the bacteria that live on our skin, or make them resistant to doxycycline (for example staph)?
- Will doxy-PEP increase doxycycline resistance in bacteria that cause STIs?
  - Although doxycycline has been used 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

Patient Decision Aids





How Do I Follow Patients on Doxy-PEP?

Follow-up

- Visits every 3-6 months
  - Repeat HIV and STI screening
  - Assess for side effects
  - Repeat counseling
  - Re-assess need for prevention modalities
  - Prescribe as appropriate

Treatment As Needed

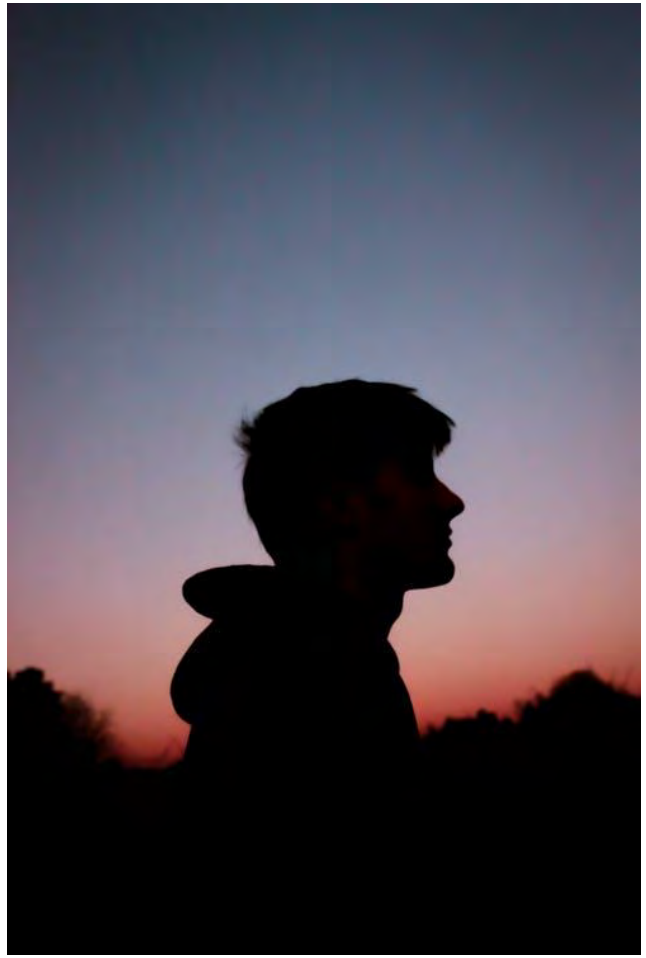
- Treat as per the 2021 STI Guidelines
  - ***Consider in-person and exam and deferring empiric treatment for "exposure"***

Clinical Conundrums

- What do I do if?
  - My patients test comes back positive for chlamydia after I've prescribed Doxy-PEP?
  - My patient is taking Doxy-PEP incorrectly
  - My patient's partner was diagnosed with an STI

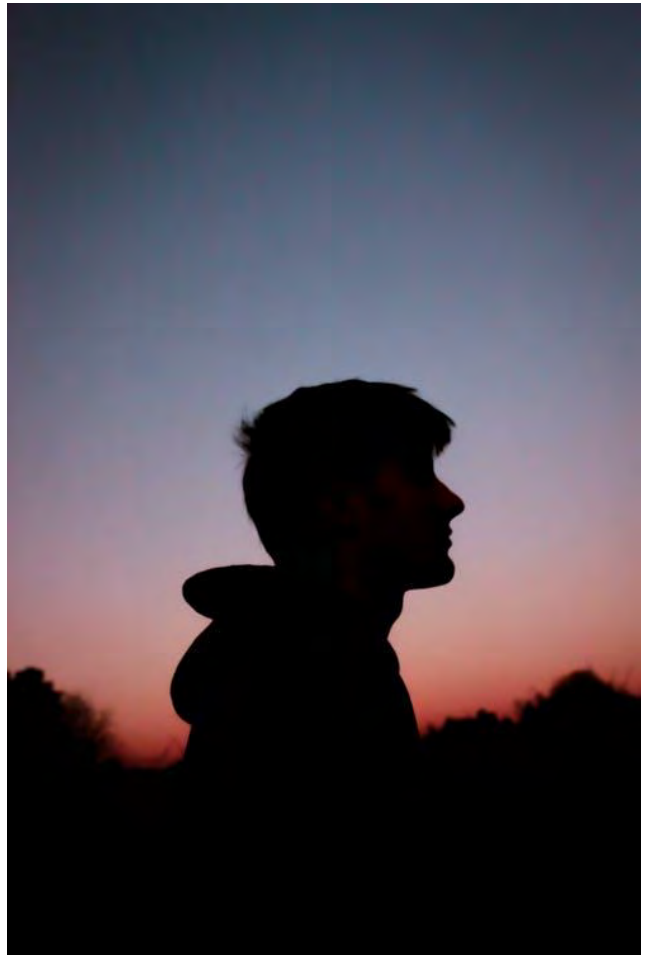
Marcus

- Marcus starts Doxy-PEP



Marcus 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



Marcus'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

Marcus's Gonorrhea Culture

Lab results:

Azithromycin – susceptible (MIC 0.125)

Ciprofloxacin – resistant (MIC 1)

Ceftriaxone – susceptible (MIC 0.016)

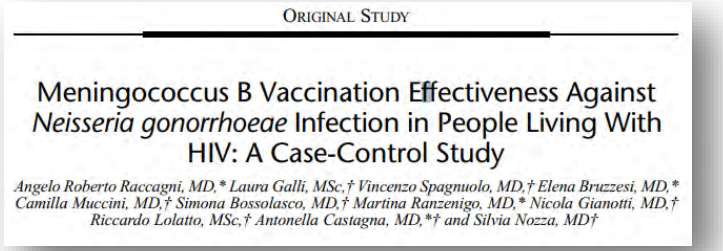
Cefixime – Susceptible (48mm)

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†*

Pop: MSM living with HIV

Efficacy: 44% (9-65%)

Location: Italy

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

Pop: Age 16 - 23

Efficacy: 40% (23-53%)

Location: USA (East Coast)

JAMA Network | Open.

Research Letter | Infectious Diseases

Association of Group B Meningococcal Vaccine Receipt With Reduced Gonorrhea Incidence Among University Students

Steve G. Robison, MPH; Richard F. Lernan, MD, MPH

Pop: College students

Efficacy: 47% (13%-68%)

Location: Australia

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

Katia J. Bruxvoort, Joseph A. Lewnard, Lie H. Chen, Hung Fu Tseng, Jennifer Chang, Jennifer Veltman, Jeanne Marrazzo, and Lei Qian

Pop: Teens and Young Adults

Efficacy: 46% (24-66%)

Location: USA (West Coast)

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

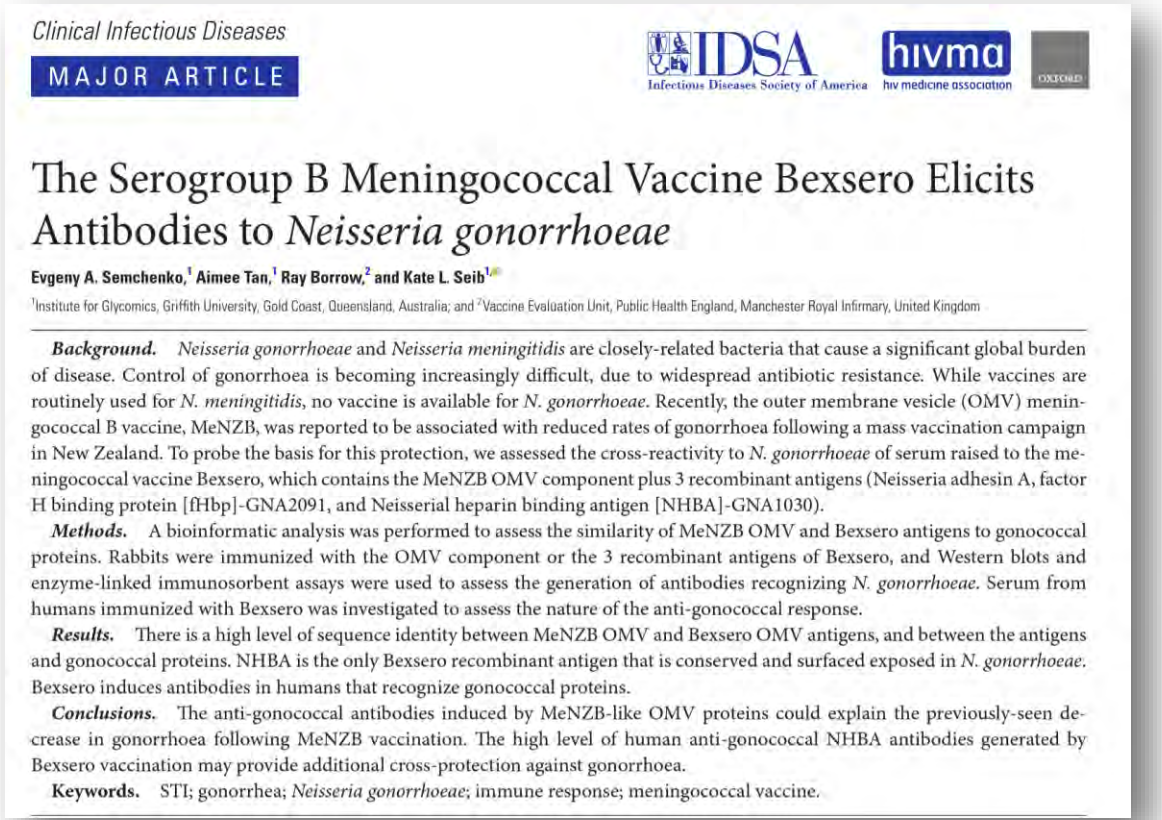
Abara WE, Bernstein KT, Lewis FMT, et al. Effectiveness of a serogroup B outer membrane vesicle meningococcal vaccine against gonorrhoea: a retrospective observational study. Lancet Infect Dis. 2022;22(7):1021-1029. doi:10.1016/S1473-3099(21)00812-4

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

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

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

DoxyVac Study Published

Doxycycline prophylaxis and meningococcal group B vaccine to prevent bacterial sexually transmitted infections in France (ANRS 174 DOXYVAC): a multicentre, open-label, randomised trial with a 2 × 2 factorial design

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Summary

Background Increased rates of sexually transmitted infections (STIs) are reported among men who have sex with men (MSM) and new interventions are needed. We aimed to assess whether post-exposure prophylaxis (PEP) with doxycycline could reduce the incidence of chlamydia or syphilis (or both) and whether the meningococcal group B vaccine (4CMenB) could reduce the incidence of gonorrhoea in this population.

Methods ANRS 174 DOXYVAC is a multicentre, open-label, randomised trial with a 2×2 factorial design conducted at ten hospital sites in Paris, France. Eligible participants were MSM aged 18 years or older, HIV negative, had a history of bacterial STIs within the 12 months before enrolment, and who were already included in the ANRS PREVENIR study (a cohort of MSM using pre-exposure prophylaxis with tenofovir and emtricitabine for HIV prevention). Participants were randomly assigned (2:1) to doxycycline PEP (two pills of 100 mg each orally within 72 h after condomless sex, with no more than three doses of 200 mg per week) or no PEP groups and were also randomly assigned (1:1) to the 4CMenB vaccine (GlaxoSmithKline, Paris, France; two intramuscular injections at enrolment and at 2 months) or no vaccine groups, using a computer-generated randomisation list with a permuted fixed block size of four. Follow-up occurred for at least 12 months (with visits every 3 months) up to 24 months. The coprimary outcomes were the risk of a first episode of chlamydia or syphilis (or both) after the enrolment visit at baseline for the doxycycline intervention and the risk of a first episode of gonorrhoea starting at month 3 (ie, 1 month after the second vaccine dose) for the vaccine intervention, analysed in the modified intention-to-treat population (defined as all randomly assigned participants who had at least one follow-up visit). This trial is registered with ClinicalTrials.gov, NCT04597424 (ongoing).

Findings Between Jan 19, 2021, and Sept 19, 2022, 556 participants were randomly assigned. 545 (98%) participants were included in the modified intention-to-treat analysis for the doxycycline PEP and no PEP groups and 544 (98%) were included for the 4CMenB vaccine and no vaccine groups. The median follow-up was 14 months (IQR 9–18). The median age was 40 years (34–48) and all 545 participants were male. There was no interaction between the two

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For the French translation of the abstract see Online for appendix 1 (p 1)

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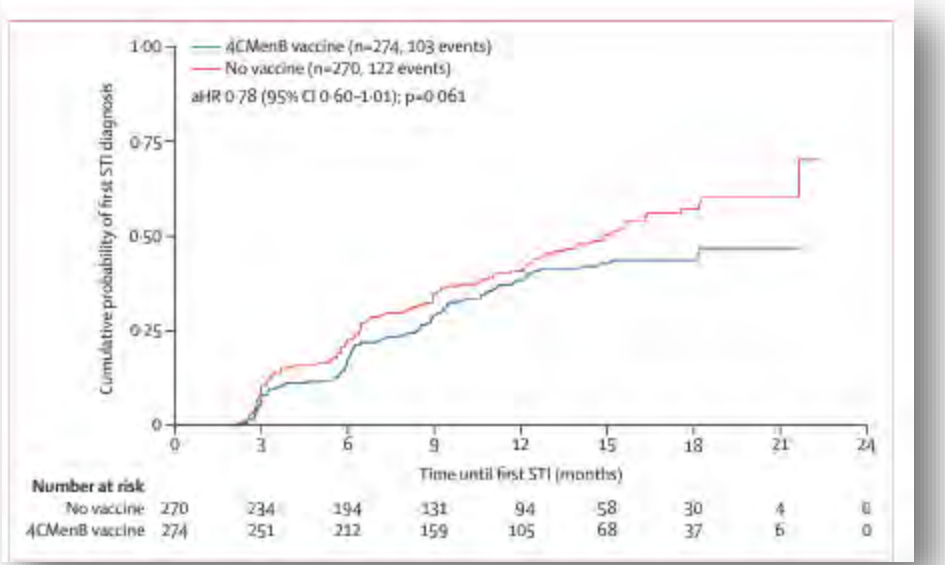

"…we **did not show efficacy** of the 4CmenB vaccine for gonorrhoea."

- https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(24)00236-6/fulltext

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 **did not work** to prevent STIs in persons assigned female at birth in the Kenyan study
  - There remain unknowns about the overall impact, risks, and unintended consequences of Doxy-PEP that potential users should be aware of (**Shared Decision Making**)
- Flexibility is key, management will change as we learn more
- **Research is needed to help us better understand the risks and benefits of different STI prevention modalities**

Questions


STI PREVENTION LANDSCAPE
Primary Prevention
Condoms
Risk Reduction Counseling
Vaccination
Medication Prophylaxis
Secondary Prevention
Routine Screening
Syndromic Testing/Treatment
Presumptive Treatment
Partner Services/EPT