

The background of the slide is a light gray gradient with several realistic water droplets of various sizes scattered across it. The droplets have highlights and shadows, giving them a three-dimensional appearance.

Doxycycline for bacterial STI prevention

**Troy Grennan, MD MSc FRCPC DTM&H
Physician Lead, HIV/STI Program, BC Centre for Disease Control
Clinical Associate Professor, Infectious Diseases, UBC**

**CATIE Webinar
22 February 2024**

Land Acknowledgment

- **WITH MUCH GRATITUDE, I ACKNOWLEDGE THAT I LIVE, WORK, AND PLAY ON THE ANCESTRAL, TRADITIONAL AND UNCEDED TERRITORIES OF THE COAST SALISH PEOPLES, AND MORE SPECIFICALLY OF THE X^wMƏθKWƏY'ƏM (MUSQUEAM), SKWXWÚ7MESH (SQUAMISH), AND SELÍLWITULH (TSLEIL-WAUTUTH) NATIONS.**



Disclosures

- Site investigator on studies funded by Merck and MedMira (funds paid to institution).
- Health Professional Investigator Award from Michael Smith Health Research BC
- Vice-Chair of PHAC's National Advisory Committee on STBBI
- *I will be discussing the off-label use of doxycycline for STI prevention*

Outline

- Background
- Summary of studies to date
- Implementation issues
 - Antimicrobial resistance
 - Microbiome impacts
 - Future work: DISCO
- The way forward ...

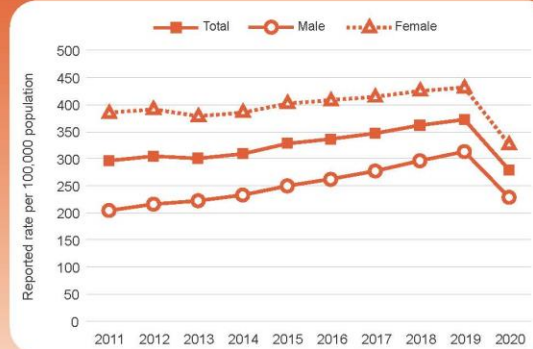
Chlamydia, Gonorrhoea and Infectious Syphilis in Canada, 2020

In the last decade, rates of chlamydia, gonorrhoea and infectious syphilis have been rising. Between 2011 and 2019, rates have increased by 26% for chlamydia, 171% for gonorrhoea, and 389% for infectious syphilis.

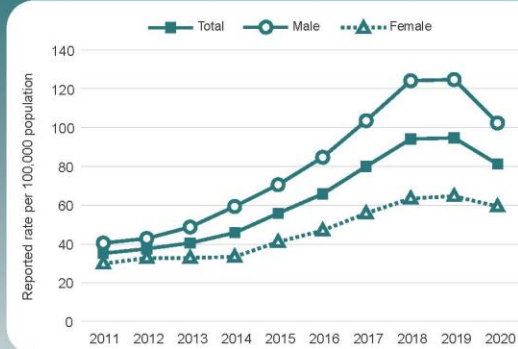
The COVID-19 pandemic affected the demand for and access to services related to sexually transmitted and blood-borne infections, including testing*. This likely impacted new chlamydia, gonorrhoea and infectious syphilis diagnosis rates in 2020.

Increases of **26%** in chlamydia, **171%** in gonorrhoea, and **389%** in syphilis in last decade.

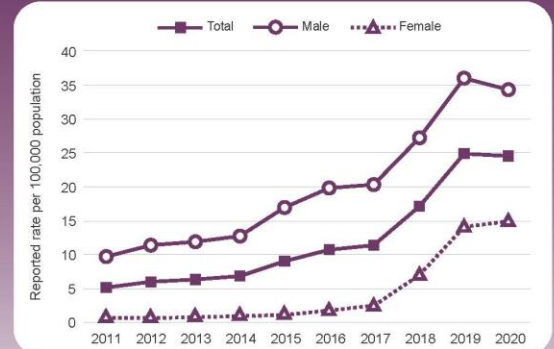
CHLAMYDIA



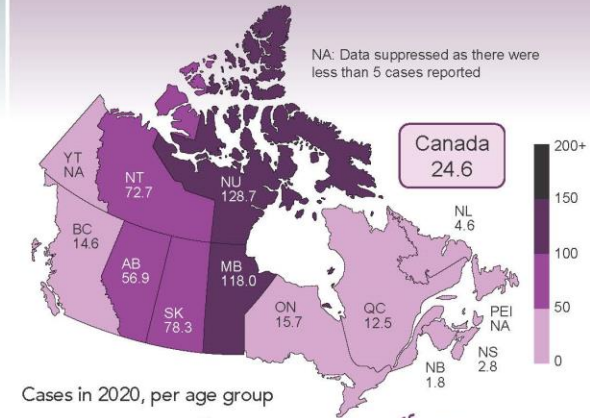
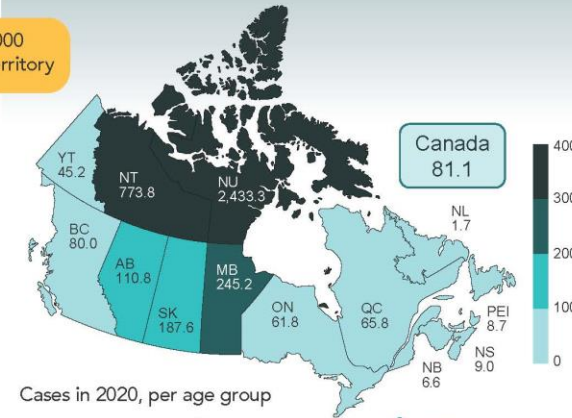
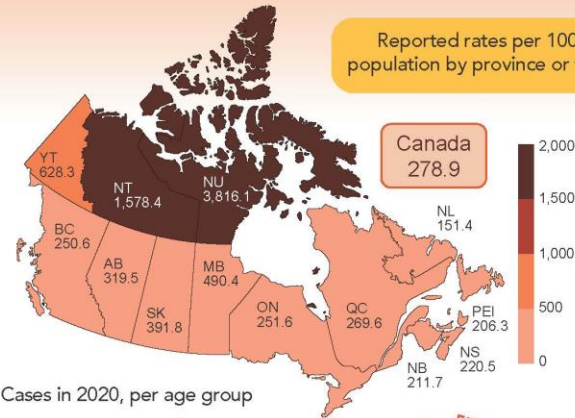
GONORRHEA



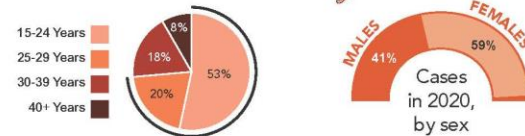
INFECTIOUS SYPHILIS



Reported rates per 100,000 population by province or territory



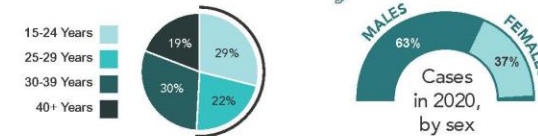
Cases in 2020, per age group



73% of chlamydia cases were among people less than 30 years of age.

Chlamydia remains the most commonly reported sexually transmitted infection

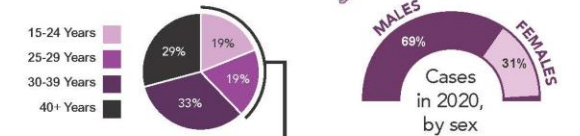
Cases in 2020, per age group



51% of gonorrhoea cases were among people less than 30 years of age.

Antimicrobial resistance in gonorrhoea remains an important public health concern

Cases in 2020, per age group



38% of infectious syphilis cases were among people less than 30 years of age.

Increasing rates of infectious syphilis in females have led to increased counts of congenital syphilis

For more information, visit [Canada.ca/STBBI](https://www.canada.ca/stbbl)
Data source: Public Health Agency of Canada, "Notifiable Disease Online," 2022 [Online]. Available at: <https://diseases.canada.ca/notifiable>

* Survey of the impact of COVID-19 on the ability to provide STBBI prevention, testing and treatment including harm reduction services in Canada. Public Health Agency of Canada, Centre for Communicable Diseases and Infection Control. 2021. Retrieved December 2022, from <https://www.canada.ca/en/public-health/services/publications/diseases-conditions/survey-impact-covid-19-delivery-stbbl-prevention-testing-treatment.html>

Emerging Paradigm: Doxycycline for Bacterial STI Prevention

SCIENCE HEALTH CARE PUBLIC HEALTH

There's a morning-after pill to prevent sexually transmitted infections

The CDC is getting close to recommending it to prevent STIs like chlamydia and syphilis.

By Keren Landman | @landmanspeaking | Updated Oct 13, 2023, 8:53am EDT

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Stay one step ahead with doxy-PEP

Did you know that doxycycline post-exposure prophylaxis (doxy-PEP) is an effective way to prevent sexually transmitted infections (STIs)?

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A note on terms used

- **DoxyPrEP:** the use of *daily* doxycycline (100mg) for STI prevention
- **DoxyPEP:** the use of doxycycline 200mg taken *after* a sexual encounter to prevent STIs
 - Generally, the sooner the better, but within 72hours
 - Different studies use different maximum # of doses

DoxyPrEP: doxycycline 100mg PO daily

Data from 2 pilot studies, totaling 82 participants.
Promising, but not powered for efficacy.

THE REAL WORLD OF STD PREVENTION

Doxycycline Prophylaxis to Reduce Incident Syphilis among HIV-Infected Men Who Have Sex with Men Who Continue to Engage in High-Risk Sexual Behavior: A Randomized, Controlled Pilot Study

Robert K. Bolan, MD,* Matthew R. Beymer, MPH,*† Robert E. Weiss, MD,‡ Arleen A. Leibowitz, PhD,§ and Jeffrey D. Klausner, MD,¶

Background: Incident syphilis infections continue to be especially prevalent among a core group of HIV-infected men who have sex with men (MSM). Because of synergy between syphilis and HIV infections, innovative means for controlling incident syphilis infections are needed.

Methods: Thirty MSM who had syphilis twice or more since their HIV diagnosis were randomized to receive either daily doxycycline prophylaxis or contingency management (CM) with incentive payments for remaining free of sexually transmitted diseases (STDs). Participants were tested for the bacterial STDs gonorrhea (*Neisseria gonorrhoeae*), chlamydia (*Chlamydia trachomatis*) and syphilis at weeks 12, 24, 36, and 48 and completed a behavioral risk questionnaire during each visit to assess

population. A randomized clinical trial should be conducted to confirm and extend these findings.

The US Centers for Disease Control and Prevention reported that the prevalence of primary and secondary syphilis was 2.6% among HIV-uninfected men who have sex with men (MSM) and 10.1% among HIV-infected MSM seen at sexually transmitted disease (STD) clinics in 2011.¹ In 2012, 75% of primary and secondary syphilis cases occurred in MSM.² A 2009 study among a population of 4376 HIV-infected MSM found that 43.6% of the cases of syphilis were diagnosed in only 3.8% of the

SCIENCE SPOTLIGHT™

Doxycycline in MSM on Prevention of Sexually Transmitted Infections The DuDHS Study

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British Columbia Centre for Disease Control and the University of British Columbia
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Disclosure: This study was partially supported by funds given directly to the Principal Investigator's institution (UBC).

CROI
2021

DoxyPEP: doxycycline 200mg within 72h of sex

Data from 3 large studies,
totaling 1279
participants,
demonstrating significant
reductions in all STI in
MSM and transgender
women.

Lancet Infect Dis 2018; 18: 308-311

Articles



Post-exposure prophylaxis with doxycycline for sexually transmitted infections in men: an open-label randomised controlled trial (IPERGAY trial)

Jean-Michel Molina, Isabelle Charreau, Christian Chidiac, Gilles Pialoux, Julien Fonsart, Béatrice Bercot, Cécile Bébéar, Laurent Cotte, Olivier Launay, Laurence Niedbalski, Bruno Spire, Luis Sagaon-Teyssier, Diane Carey, for the ANRS IPERGAY Study Group*

Summary

Background Increased rates of sexually transmitted infections in 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

ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Use of Doxycycline to Prevent Sexually Transmitted Infections

Stephanie Cohen, M.D., M.P.H., Deborah Donnell, Ph.D., Clare E. Brown, Ph.D., Cheryl Malinski, B.S., Melody Nasser, B.A., Carolina Lopez, B.A., Hyman Scott, M.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*

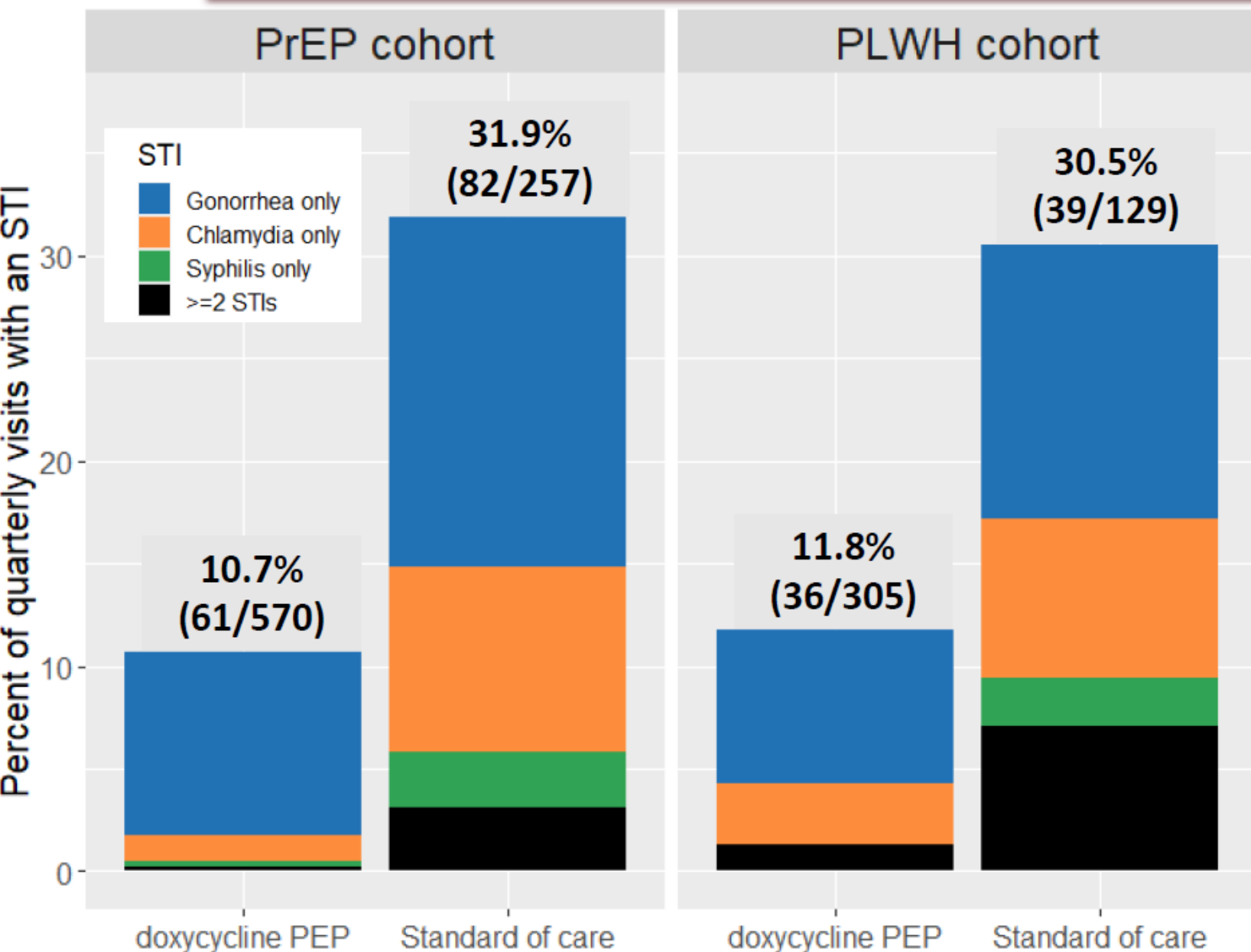
Lancet Infect Dis 2018; 18: 308-17
Published Online
December 8, 2017
[http://dx.doi.org/10.1016/S1473-3099\(17\)30725-9](http://dx.doi.org/10.1016/S1473-3099(17)30725-9)

See [Comment](#) page 233

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

New Engl J Med 2023; 388: 1296-1306.

Primary Endpoint: STI incidence per quarter



Reduction in STI incidence/quarter	
risk reduction (95% CI)	
PrEP	0.34 (0.24 - 0.46)
Living with HIV	0.38 (0.24 - 0.60)
Total	0.35 (0.27 - 0.46)

all p < 0.0001

Slide courtesy of A Luetkemeyer

Reduction in each STI per quarter

risk reduction (95% CI)

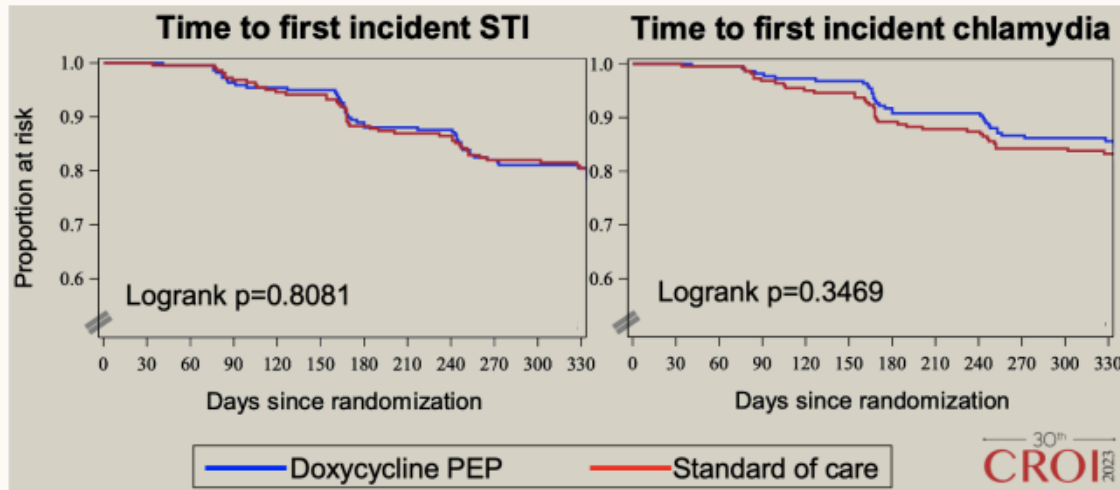
	PrEP	PLWH
GC	0.45 ↓55% (0.32 - 0.65) <i>p</i> <0.0001	0.43 ↓57% (0.26 - 0.71) <i>p</i> =0.001
CT	0.12 ↓88% (0.05 - 0.25) <i>p</i> <0.0001	0.26 ↓74% (0.12 - 0.57) <i>p</i> =0.0007
Syphilis	0.13 ↓87% (0.03 - 0.59) <i>p</i> =0.0084	0.23 ↓77% (0.04 - 1.29) <i>p</i> =0.095

And one more!

DPEP KENYA TRIAL RESULTS



Analysis	Endpoint	Total	PEP (N=224)	SOC (N=225)	RR	95% CI	P-value
Intention to Treat	All STIs	109	50	59	0.88	0.60-1.29	0.51
	Chlamydia	85	35	50	0.73	0.47-1.13	0.16
	Gonorrhea	31	19	12	1.64	0.78-3.47	0.19
Censoring Pregnancy Time	All STIs	105	48	57	0.91	0.62-1.35	0.65
	Chlamydia	82	33	49	0.73	0.46-1.15	0.18



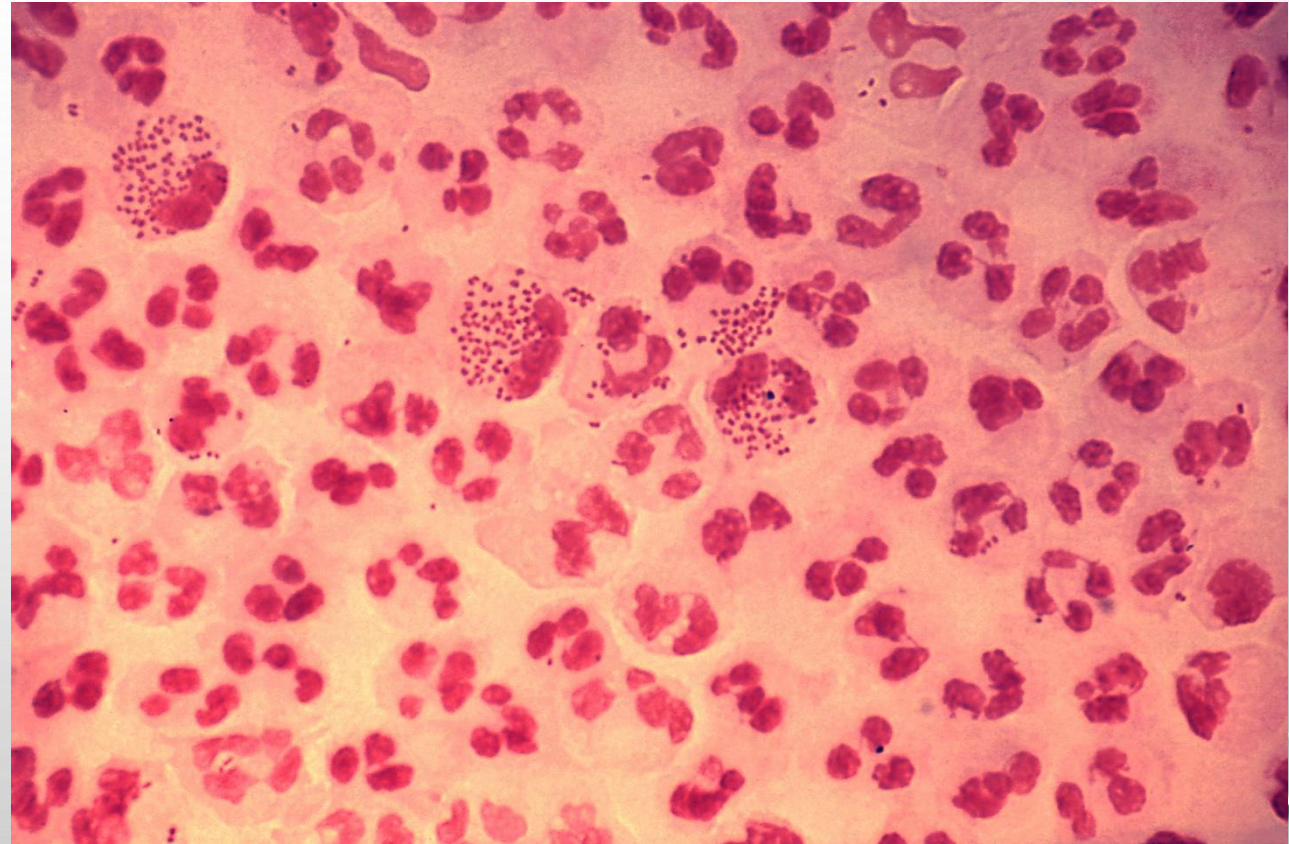
Slide courtesy of J Stewart

DoxyPEP and DoxyPrEP: Unanswered Questions and Unresolved Issues

1. Why the differential impact on gonorrhoea?
2. What is the impact of doxycycline on antimicrobial resistance (AMR)?
3. What is the impact of doxycycline on the human microbiome?
4. How does/will DoxyPEP and DoxyPrEP perform in other populations?
5. What future work is planned?

1. Why the differential impact on gonorrhoea?

- Overall, some conflicting results:
 - IPERGAY: no effect
 - DoxyPEP and DOXYVAC: effect, but dampened (vs syphilis, chlamydia)
- Different rates of resistance in US (~30%) vs. France (~60%).
- From later French study suggests that in context of high baseline resistance, likely still a preventative role to play.



2. What is the impact of doxycycline on AMR?

- Little data from completed studies
- AMR to tetracyclines never documented in syphilis or chlamydia
- Need to consider AMR in ‘off-target’ organisms
- Systematic review:
 - Increased burden in oral, respiratory and GI; no persistent AMR seen. Poor data quality.

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

Robinson Truong^{1,2}, Vincent Tang¹, Troy Grennan^{3,4} and Darrell H. S. Tan^{1,2,5,6*}

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*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.

2. What is the impact of doxycycline on AMR?

AMR IN GONORRHEA

- **DoxyPEP Study**
 - Baseline: 4/15 (27%) AMR in NG to tetracyclines
 - DoxyPEP group: 5/13 (38%) AMR in NG to tetracyclines
 - Std of care group: 2/16 (12%) AMR in NG to tetracyclines
- **Doxyvac Study**
 - All 65 cultures of NG demonstrated AMR to tetracyclines

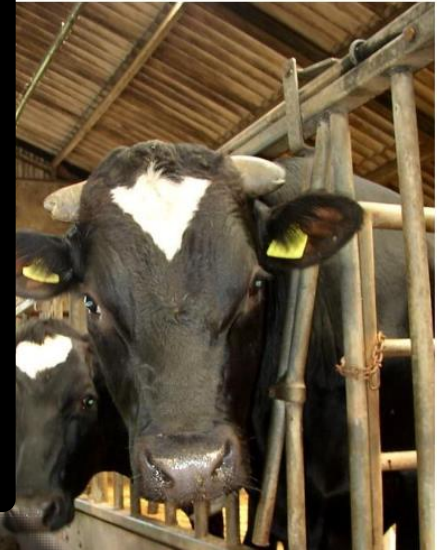
AMR IN OFF-TARGET BUGS

- **DoxyPEP Study**
 - DoxyPEP group: lower *S. aureus* carriage; marginally higher rates of AMR to tetracyclines (5% vs 4%).
- **DuDHS Study**
 - Low *S. aureus* carriage (9 in IMM arm; 12 in DEF arm)
 - AMR in 5 isolates in IMM and 1 in DEF ($p = 0.077$)

AMR: Food for thought



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3. What is the impact of doxycycline on the human microbiome?

- No published data yet
- From the DuDHS study, there were no significant changes in microbial taxa observed between study arms, though limited by small participant numbers.

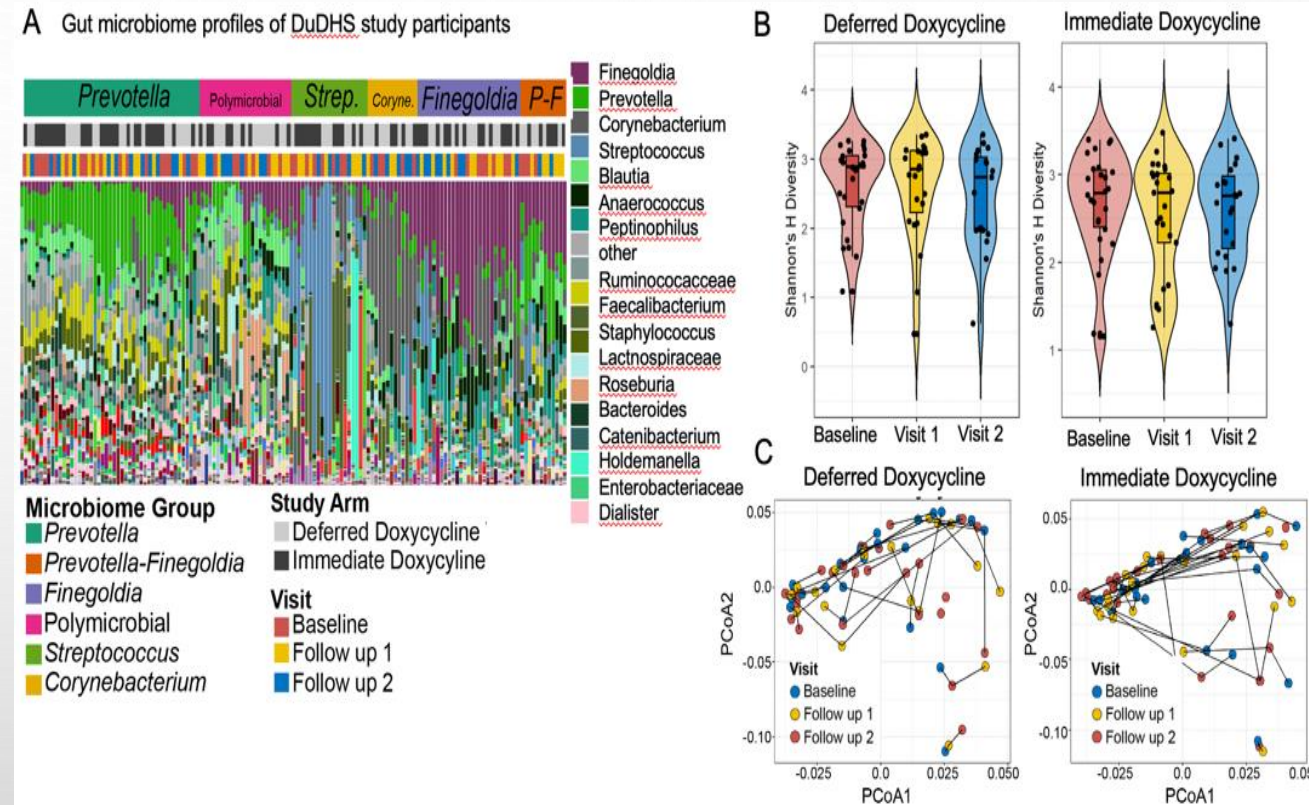


Figure 1. Gut microbiome composition of study participants in the DuDHS study. (A) This plot shows overall microbial composition diversity of samples from the study participants (n=52), and dominant taxa are indicated on the top; (B) Violin plots in each study arm (n=26 in each) shows no significant changes in alpha diversity (Shannon's H) compared to baseline ($P>0.05$); (C) A PCoA plot of individual microbiome composition shows no separation by time in study. There were no individual taxa that changed over time that passed an FDR threshold of $P<0.05$ in either study arm.

4. How does/will DoxyPEP and DoxyPrEP perform in other populations?

- One study (dPEP Kenya) showed no effect of DoxyPEP on STIs in cisgender females on HIV PrEP – likely related to adherence.
- Outstanding questions:
 - Efficacy in different contexts/populations (e.g. youth)?
 - Role for enhanced adherence measures?
 - Role for DoxyPrEP?

Discussion

Doxycycline PEP is only indicated after sexual exposures and sexual activity cannot be measured beyond self-report

Self-reported adherence was moderately high with full coverage including all correct use: no doxycycline use if no sexual exposures.

Doxycycline hair testing indicated that 44% assigned to doxycycline PEP may not have taken any doxycycline.



5. What future work is planned?



Doxycycline Intervention for STI ChemOprophylaxis

- N = 560
- Randomized 1:1 to doxyPrEP vs doxyPEP
- Study sites: Vancouver, Calgary, Hamilton, Toronto, Ottawa, Montreal

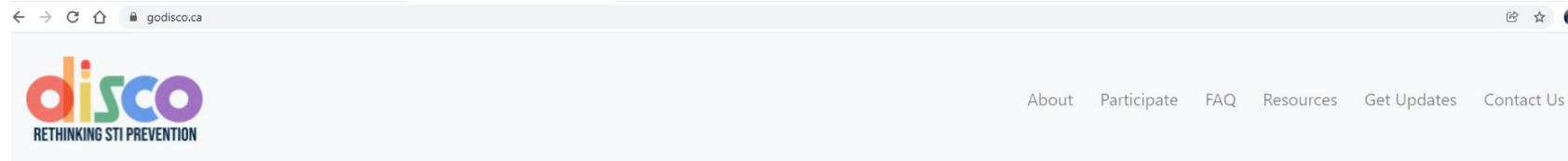


ELIGIBILITY CRITERIA

- Aged ≥ 18 years;
- Identify as MSM (cis or trans) or transgender woman;
- Sexually active with ≥ 1 male partner in last 12 months;
- Intend to remain sexually active; **AND**
- ≥ 1 CT, GC or syphilis infection in last 12 months.



- Began enrolment at our Vancouver site mid-June; Calgary site started more recently
 - ~95 participants recruited so far
 - National enrolment goal = 560



The Way We Think About STI Prevention & Treatment Is Changing

Infection rates for bacterial sexually transmitted diseases (STIs) like syphilis, chlamydia and gonorrhea are on the rise, and gay, bisexual, and other men who have sex with men and transgender women are being disproportionately affected.

The waning effectiveness of conventional STI prevention tools like condoms and the potential development of serious complications from these STIs signals the need for new STI prevention strategies and tools.



The way forward

- Efficacy for DoxyPEP in MSM and trans women established
- Work still required around implementation
 - How best to provide this? e.g. at point of care
 - Acceptability
 - Cannot limit only to HIV+ or PrEP users; STI dx is better guide
 - Guidelines – few local ones currently; US CDC pending; PHAC TBD.
 - How best to measure AMR and microbiome impacts



POPULATION HEALTH DIVISION
SAN FRANCISCO DEPARTMENT OF PUBLIC HEALTH



Health Update

Doxycycline Post-Exposure Prophylaxis Reduces Incidence of Sexually Transmitted Infections

October 20, 2022

Situational Update

Researchers at San Francisco General, recently collaborate (PEP) of sexually transmitted infections (STIs) within 72 hours after exposure to HIV and transgender women. HIV and PrEP prophylaxis (HIV PEP) acquisition of chlamydia.

Participants on PrEP and 62% of participants randomized to doxycycline PEP were recently prescribed. STI resistance in bacterial microbiome.

The CDC has not yet determined if off-label STI prophylaxis is an urgent public health issue. Many providers in SFPDHP are providing PEP in MSM and TGW.



PUBLISHING

POSITION STATEMENT
<https://doi.org/10.1071/SH23011>

SEXUAL HEALTH

Interim position statement on doxycycline post-exposure prophylaxis (Doxy-PEP) for the prevention of bacterial sexually transmissible infections in Australia and Aotearoa New Zealand – the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM)

Vincent J. Cornelisse^{A,B,C,D,*}, Jason J. Ong^{A,B,E,F}, Nathan Ryder^{A,B,G,H}, Catriona Ooi^{A,I,J}, Arthur Wong^{B,K}, Penny Kenchington^{A,L}, Massimo Giola^M, Basil Donovan^B, Judith A. Dean^{A,N}, Jean-Michel Molina^O and Nicholas A. Medland^{A,B,C}

For full list of author affiliations and declarations see end of paper.

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Handling Editor:
Christopher Fairley

ABSTRACT

Recent studies have provided evidence for the effectiveness of using doxycycline (Doxy-PEP) to prevent bacterial sexually transmissible infections (STI), namely chlamydia, gonorrhoea, and syphilis, among gay, bisexual, and other men who have sex with men who have experienced multiple STIs. However, there remain several unanswered questions around potential adverse outcomes from Doxy-PEP, including the possibility of inducing antimicrobial resistance in STIs and other organisms, and the possibility of disrupting the microbiome of people who choose to use Doxy-PEP. This interim position statement from the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine aims to outline the current evidence for Doxy-PEP, and to highlight potential adverse outcomes, to enable clinicians to conduct evidence-based conversations with patients in Australia and Aotearoa New Zealand who intend to use Doxy-PEP.

Keywords: Australia, chlamydia, doxycycline, gonorrhoea, men who have sex with men, New Zealand, prevention, STIs, syphilis.

Introduction

Acknowledgments

- **Study participants**
- **DISCO Co-PIs**: A Burchell, M Hull, D Tan
- **DISCO Study Team**: A Burgener, A Chu, B Cameron, J Cox, J Edward, M Gilbert, J Gill, J Gillis, D Hall, W Isaranuwachai, R Lester, P Macpherson, S Mishra, M Morshed, S Poulin, M Romney, C Shukalek, J Singer, P Smyczek, S Stone, L Wang, J Wong.
- **DISCO Community Advisory Board**: J Edward, J Dame, J Bacon, V Mousseau, A Sylliboy
- **Staff at all participating sites** in Vancouver, Calgary, Hamilton, Toronto, Ottawa, and Montreal.
- **Funders**: Canadian Institutes for Health Research (CIHR); CIHR Canadian HIV Trials Network; Michael Smith Health Research BC



Questions:

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