Doxy PEP:
The Science, Current Guidance, and Considerations for Implementation

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Envisioning a New York City without transmission or illness related to viral hepatitis, HIV, and sexually transmitted infections.

NYC Health

Overview of today's talk

- Trends in the incidence of bacterial STI in NYC
- Data from recent studies establishing the efficacy of doxy PEP in preventing bacterial STIs
- Examples of local and national guidance for doxy PEP use
- Implementation considerations

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Overview of STI reporting requirements

The Health Department receives reports from providers and laboratories for several infectious diseases, including sexually transmitted infections (STIs), as required by law in the NYC Health Code. Basic demographic information on the person being tested is reported to the Health Department, including name, address, and date of birth. The following STIs are reportable to the Health Department within 24 hours of diagnosis:

Chlamydia	**Herpes, neonatal (infants aged ≤ 60 days)**
Chancroid	**Lymphogranuloma venereum**
Gonorrhea	**Mpox**
Granuloma inguinale (donovanosis)	**Syphilis (all stages, including congenital)**

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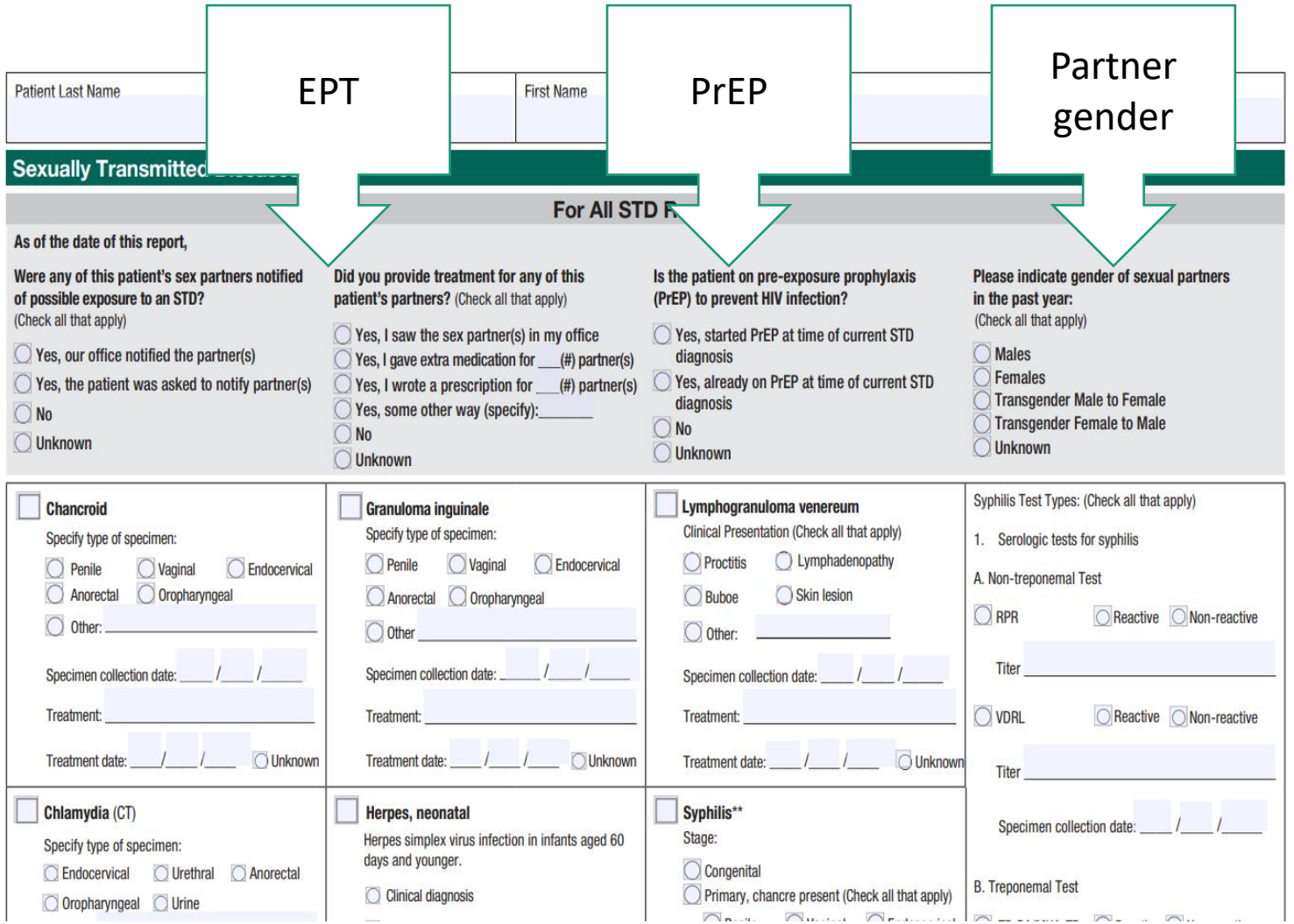
Legal Mandates Relevant to STI

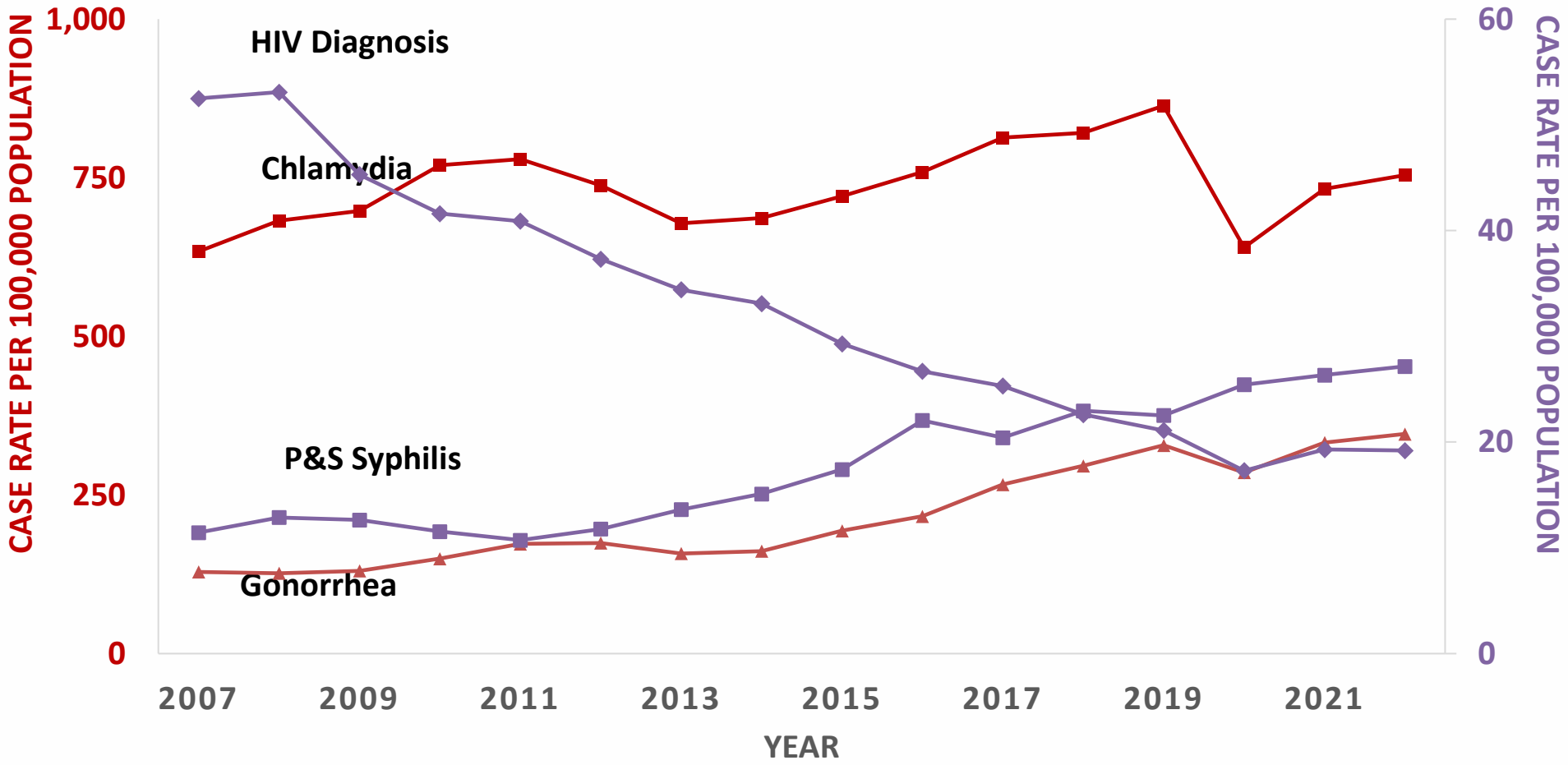
- NYC Health Code:
  - Dual provider and laboratory reporting of STI

- Provider reports contain valuable details not available on laboratory reports
  - Demographics
  - Symptoms
  - Treatment
  - Gender of sex partners
  - Partner management (including EPT)
  - PrEP use

32% lab-reported cases have a provider report



Reported chlamydia, gonorrhea, primary and secondary syphilis, and HIV diagnosis, case rates (per 100,000), New York City, 2007-2022



STIs rising while HIV diagnoses decline in NYC

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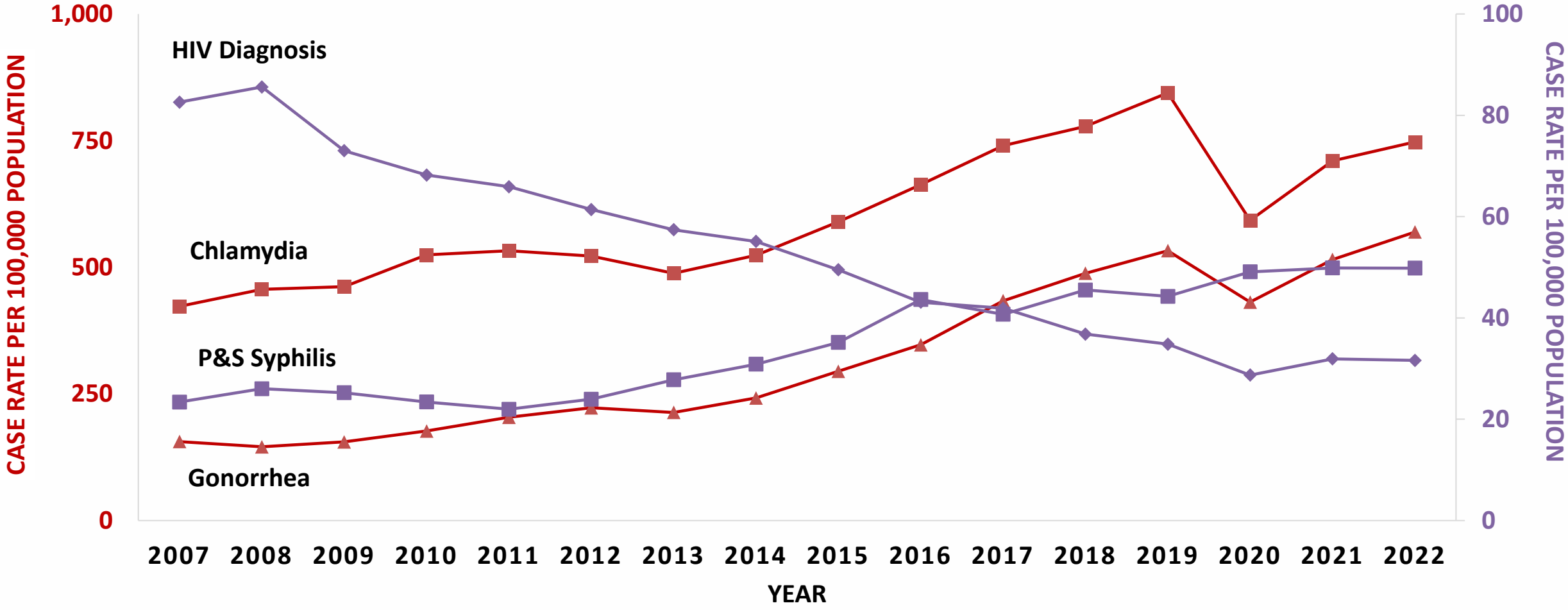
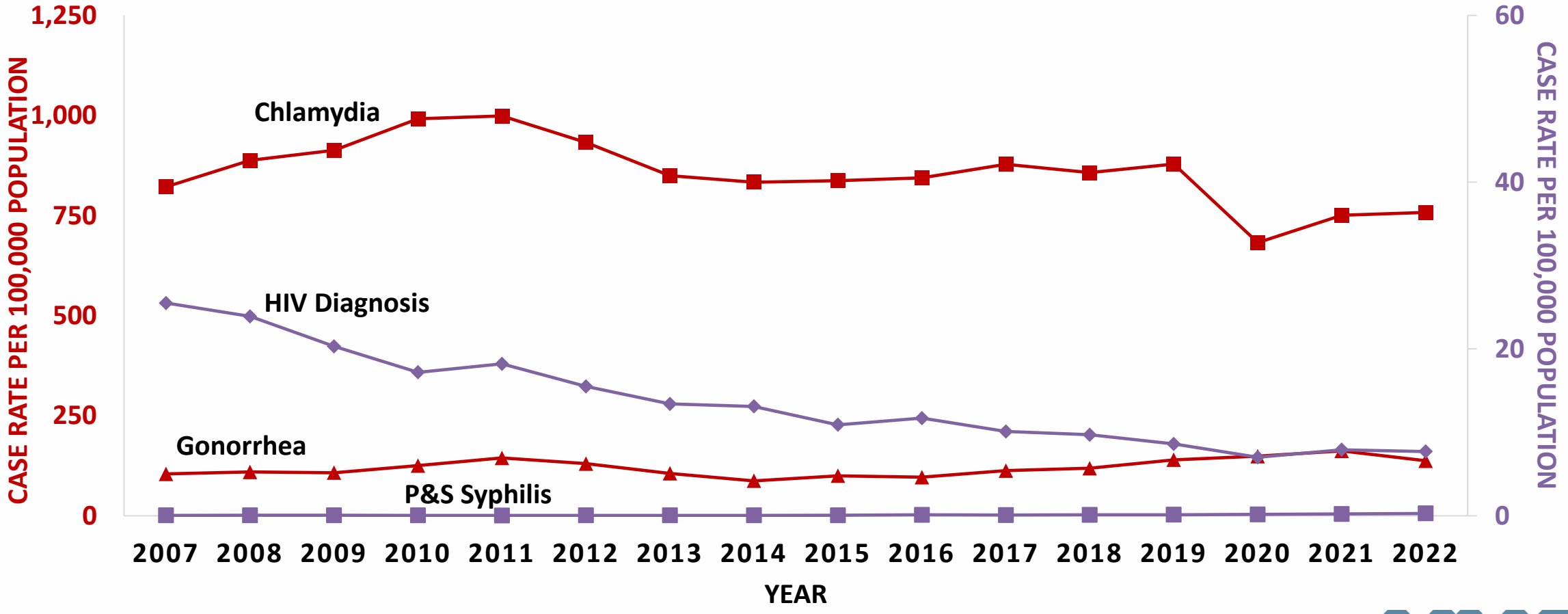
Reported male chlamydia, gonorrhea, primary and secondary syphilis, and HIV diagnosis, case rates (per 100,000), New York City, 2007-2022



Health

Reported female chlamydia, gonorrhea, primary and secondary syphilis, and HIV diagnosis, case rates (per 100,000), New York City, 2007-2022



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Doxycycline Post-Exposure Prophylaxis (doxy PEP)

Upsides

Doxycycline is safe, well tolerated, and inexpensive

Three RCTs (IPERGAY, DoxyPEP, DOXYAC) have demonstrated efficacy of doxy-PEP in preventing bacterial STIs in men who have sex with men (MSM)

Concerns

Lack of efficacy in cis women (dPEP study, Kenya)

Could increase prevalence of tetracycline-resistant gonorrhea (GC), but not used as 1st line treatment for GC

Impact of intermittent doxy use on drug resistance

Impact on microbiome

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RCTs of doxy PEP among MSM and transgender women

Select Doxy-PEP Studies Among Cisgender MSM and Transgender Women, 2018-2023					
Study	Participating Population	Rate of STIs (gonorrhea, chlamydia, syphilis)		Relative Risk Reduction in STIs	Absolute Risk Reduction in STIs
		Doxy-PEP	No Doxy- PEP		
DoxyPEP[2]	327 MSM and transgender women taking HIV pre-exposure prophylaxis (PrEP)	10.7% per quarter	31.9% per quarter	66%*	21.2% per quarter
DoxyPEP[2]	174 MSM and transgender women with HIV	11.8% per quarter	30.5% per quarter	62%*	18.7% per quarter
DoxyVac[3]	502 MSM on HIV PrEP	26.1 per 100 person-years	76.7 per 100 person-years	66%	51 per 100 person-years
IPERGAY[4]	232 MSM on HIV PrEP	37.7 per 100 person-years	69.7 per 100 person-years	47%**	32 per 100 person-years

*The study found reductions of 87% for syphilis, 88% for chlamydia, and 55% for gonorrhea among people taking HIV PrEP, and reductions of 77% for syphilis, 74% for chlamydia, and 57% for gonorrhea among people with HIV.

**Doxy-PEP did not decrease gonorrhea, likely because of the high prevalence of doxycycline-resistant gonorrhea in the population studied.

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IPERGAY

Study	Participating Population	Rate of STIs (gonorrhea, chlamydia, syphilis)		Relative Risk Reduction in STIs	Absolute Risk Reduction in STIs
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Molina JM, et al. *Lancet Infect Dis*. 2018;18(3):308-317

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DoxyPEP

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Luetkemeyer AF, et al. *N Engl J Med*. 2023;388(14):1296-1306.

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DoxyVAC

Study	Participating Population	Rate of STIs (gonorrhea, chlamydia, syphilis)		Relative Risk Reduction in STIs	Absolute Risk Reduction in STIs
		Doxy-PEP	No Doxy- PEP		
DoxyVac	502 MSM on HIV PrEP	26.1 per 100 person-years	76.7 per 100 person-years	66%	51 per 100 person-years

Molina JM et al., CROI 2023

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Doxy PEP and time to first STI

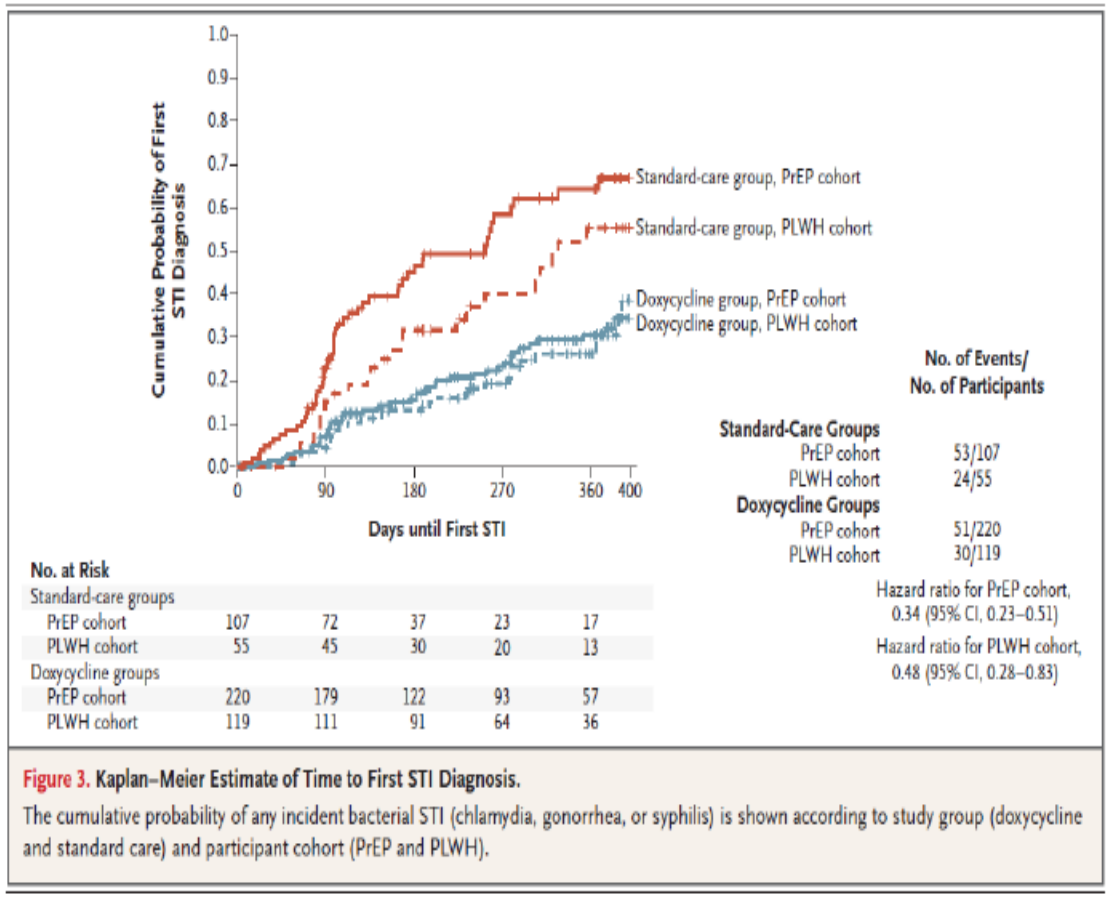


Figure 3. Kaplan–Meier Estimate of Time to First STI Diagnosis.

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).

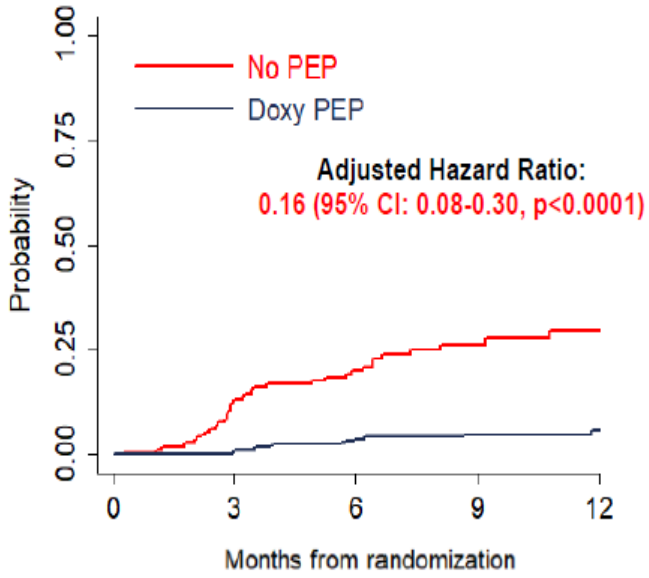
Luetkemeyer A et al. NEJM 2023

DOXYVAC: Doxycycline PEP Time to First CT or Syphilis Infection

No interaction between Doxy PEP and 4CMenB vaccine (p=0.99)

Median follow-up: **9 months** (IQR: 6 to 12)

49 subjects infected
36 in No PEP arm (incidence: 35.4/100 PY),
13 in Doxy PEP arm (incidence: 5.6/100 PY)



Number at risk

No PEP	170	137	99	47	22
Doxy PEP	332	271	220	144	83

Jean-Michel Molina, CROI 2023

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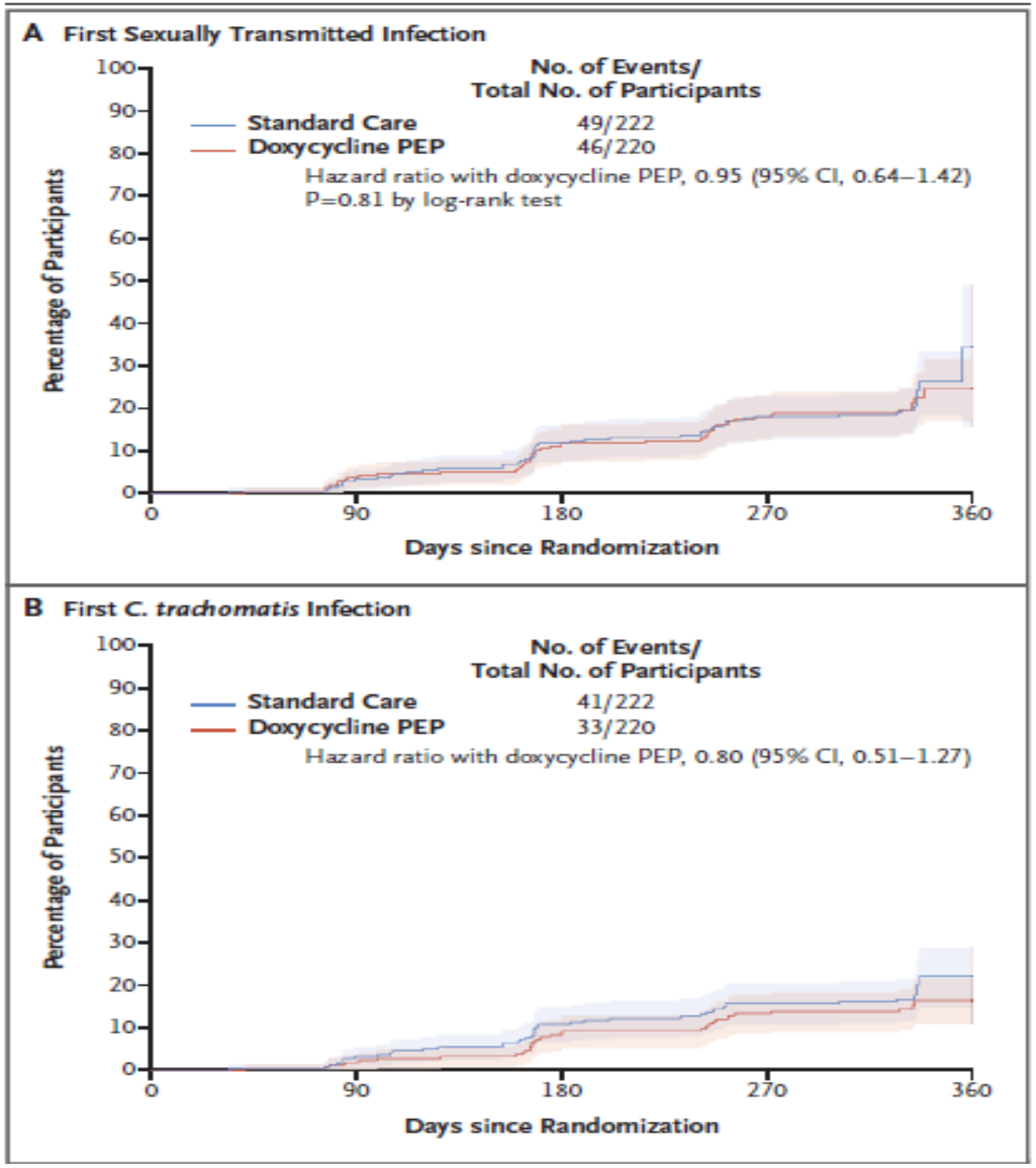
dPEP Kenya Trial

- 18% had an STI at enrollment
- Annual STI incidence = 27%
- No significant difference in incident STI events between doxy PEP and standard of care arms
  - 109 new STIs
    (50 doxy PEP, 59 standard of care)
  - 78% were chlamydial infections
    (35 doxy PEP, 50 standard of care)



Stewart J et al. *N Engl J Med* 2023;389:2331-40.

Why was doxy-PEP not effective for STI prevention in cis-women in DPEP study?

- Anatomy: Endocervical tissue may differ from urethral, rectal, and pharyngeal tissue
- Exposures: Type and frequency of STI exposures may differ in high prevalence setting, and fewer average number of partners
- Resistance: To date, no known cases of resistant *C. trachomatis* globally; however, high rates of resistant *N. gonorrhea*
- Adherence: Trial was designed to maximize adherence, and self-reported adherence was high but imperfect

Jenell Stewart, CROI 2023

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Other considerations

Safety and Adverse Events

- No doxycycline-related serious adverse events were reported in the DoxyPEP, DOXYVAC, and DuDHS studies
- Three participants in dPEP reported instances of IPV due to doxy PEP use
- Recent systematic review of 67 studies found that longer term use of doxycycline (>8 weeks) was found to be generally safe with minimal side-effects (Chan, P.A. et al, *Sex Transm Dis*, 2023)

Acceptability & attitudes towards doxycycline prophylaxis

- Multiple studies of community members and clinicians demonstrate high rates of doxy PEP acceptability
- Antimicrobial resistance concerns for some persist, and long-term safety data and official guidelines were needed to facilitate adoption

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Current real-world use – national guidance

Several health departments and other agencies have released guidelines regarding doxy PEP use with varying strength of guidance for priority populations.

Australia

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 gonorrhea might be important."

GBMSM with: a recent syphilis diagnosis; ≥2 recent other bacterial STI diagnoses (i.e., not syphilis); an upcoming period of heightened STI risk (e.g., attendance at a sex event); concurrent male and cisgender female sexual partners or other sexual partners with a uterus, recognizing the additional health risks posed by chlamydia, gonorrhea and syphilis for people with a uterus

Recommended to **use Doxy-PEP for a predefined period, e.g., 3–6 months, followed by review of the need for ongoing use**

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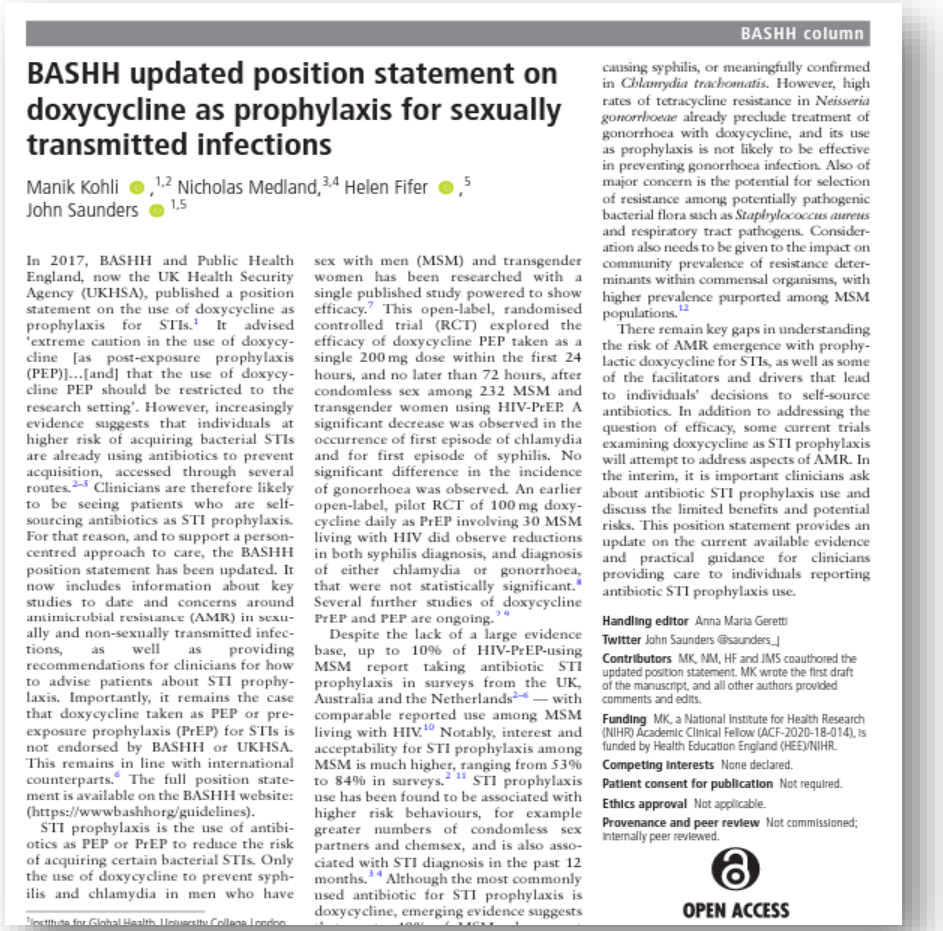
Current real-world use – national guidelines

British Association of Sexual Health and HIV



BASHH column

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

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

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

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

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

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

Handling editor Anna Maria Geretti

Twitter John Saunders @saunders_j

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

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Ethics approval Not applicable.

Provenance and peer review Not commissioned; Internally peer reviewed.

OPEN ACCESS

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

Any potential benefits will be outweighed by the considerable potential to select resistance in STI pathogens and other bacterial species

Further studies are required to measure the wider impact of prophylactic doxycycline on antimicrobial resistance at an individual and population level

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Current real-world use – jurisdictional guidance

Seattle-Kings County

Recommendations

1) Medical providers should **inform** cis-gender MSM and transgender women who have sex with men with a history of bacterial STI in the prior year about doxy-PEP, its efficacy, the potential benefits and risks of the intervention, and the alternative options available to prevent, diagnose, and treat STIs.
2) The decision to prescribe doxy-PEP should result from a **shared decision-making** process between the medical provider and the patient. Providers should give particular consideration to prescribing doxy-PEP to patients with a history of syphilis or a history of multiple STIs in the prior year. Providers may consider prescribing doxy-PEP on an episodic basis when patients anticipate periods when their risk of STI may be higher (e.g., group sex events).
3) Doxy-PEP is not recommended for cisgender women. A recent study found no effect of doxy-PEP in cisgender women in Kenya in preventing STIs.
4) The potential benefits and risks for transgender men (and other gender diverse patients assigned female sex at birth) who have anal sex with men are unknown. This population was not included in prior studies.

San Francisco

Recommendations

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

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

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Current real-world use – jurisdictional guidance

New York State

RECOMMENDATIONS

Biomedical Prevention of STIs

- Clinicians should offer doxy-PEP to cisgender men and transgender women who are taking HIV PrEP or receiving HIV care and 1) engage in condomless sex with partner(s) assigned male sex at birth and 2) have had a bacterial STI diagnosed within the past year and are at ongoing risk of STI exposure. (A1)
- Clinicians should offer doxy-PEP to cisgender men and transgender women who are *not* taking HIV PrEP or receiving HIV care and 1) engage in condomless sex with partner(s) assigned male sex at birth and 2) have had a bacterial STI diagnosed within the past year and are at ongoing risk of STI exposure. (A2†)
- Clinicians should engage in shared decision-making with cisgender men who 1) engage in condomless sex with multiple partners assigned female sex at birth and 2) have had a bacterial STI diagnosed within the past year, offering doxy-PEP on a case-by-case basis. (B3)

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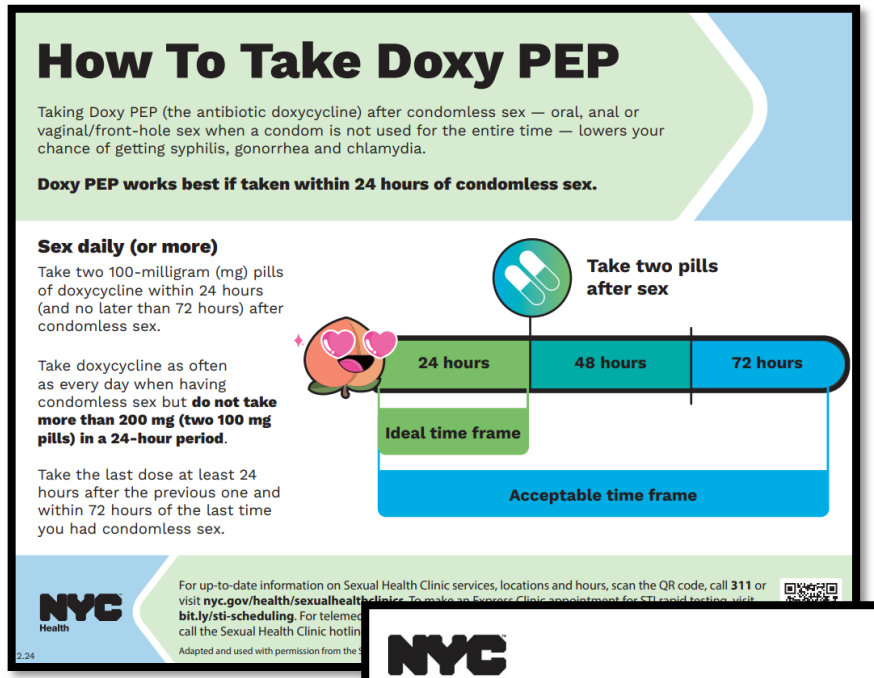
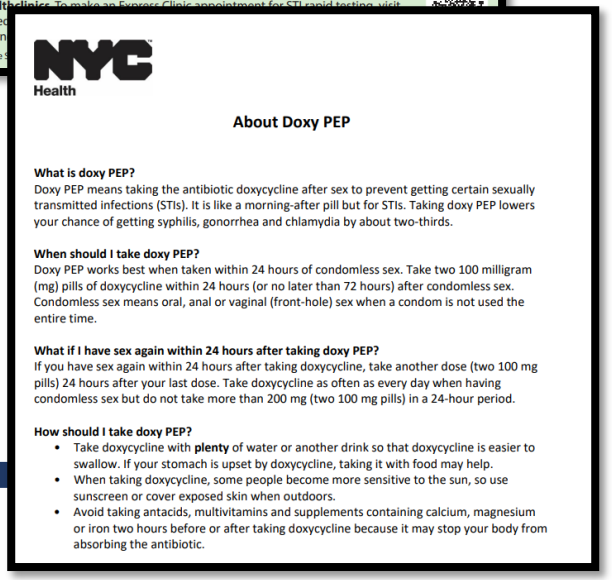
Current real-world use – local guidance

New York City

Recommendations for Health Care Providers

- **Take a comprehensive sexual history** as part of routine care for all patients to elicit information most useful for identifying an appropriate clinical course of action.[11]
- Prescribe doxy-PEP based on **shared decision-making** with the patient; provide information on its effectiveness and potential benefits and risks, as well as other options available to prevent STIs.
- **Give particular consideration to prescribing doxy-PEP to MSM and transgender women with a history of bacterial STIs in the prior year**, especially those with a history of syphilis or multiple STIs.
    - Doxy-PEP is **not recommended for cisgender women** given the lack of sufficient trial data.
    - **Transgender men and gender-diverse patients assigned female sex at birth were not included in prior studies**, and the potential benefits and risks of doxy-PEP for them are unknown.
- **Consider prescribing doxy-PEP on an episodic basis** for patients who anticipate periods when their STI risk may be higher (e.g., attendance at group sex events).

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About Doxy PEP

What is doxy PEP?
Doxy PEP means taking the antibiotic doxycycline after sex to prevent getting certain sexually transmitted infections (STIs). It is like a morning-after pill but for STIs. Taking doxy PEP lowers your chance of getting syphilis, gonorrhea and chlamydia by about two-thirds.

When should I take doxy PEP?
Doxy PEP works best when taken within 24 hours of condomless sex. Take two 100 milligram (mg) pills of doxycycline within 24 hours (or no later than 72 hours) after condomless sex. Condomless sex means oral, anal or vaginal (front-hole) sex when a condom is not used the entire time.

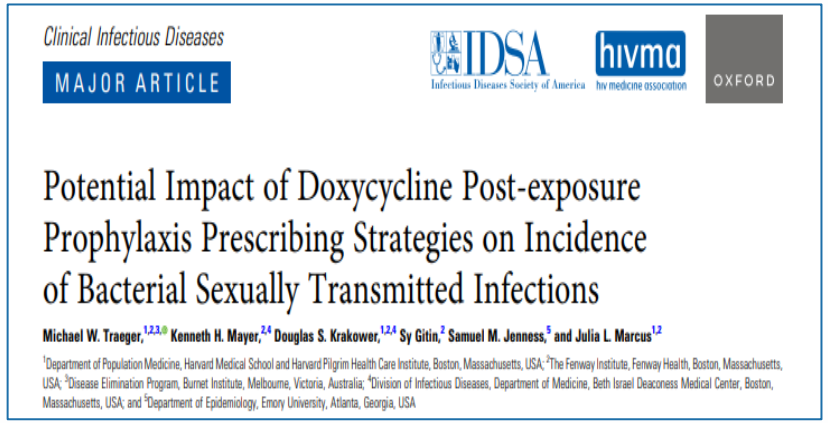
What if I have sex again within 24 hours after taking doxy PEP?
If you have sex again within 24 hours after taking doxycycline, take another dose (two 100 mg pills) 24 hours after your last dose. Take doxycycline as often as every day when having condomless sex but do not take more than 200 mg (two 100 mg pills) in a 24-hour period.

How should I take doxy PEP?
- Take doxycycline with **plenty** of water or another drink so that doxycycline is easier to swallow. If your stomach is upset by doxycycline, taking it with food may help.
- When taking doxycycline, some people become more sensitive to the sun, so use sunscreen or cover exposed skin when outdoors.
- Avoid taking antacids, multivitamins and supplements containing calcium, magnesium or iron two hours before or after taking doxycycline because it may stop your body from absorbing the antibiotic.

Modeling population impact

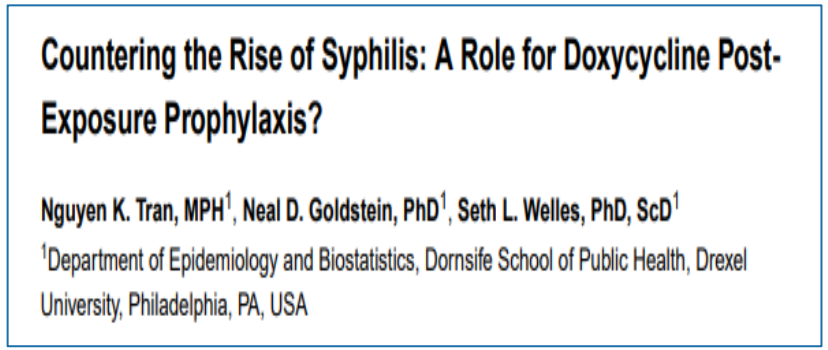
Fenway Health modeling study

- Examined 10 potential doxy PEP prescribing strategies
- Prescribing doxy PEP to individuals with STIs, particularly concurrent or repeated STIs, could avert a substantial proportion of all STI diagnoses



Philadelphia modeling study

- Agent-based models to assess population-level impact
- Uptake scenario of 20% with 80% adherence would reduce cumulative syphilis incidence by 10% over the next decade



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Equitable implementation

Racial & ethnic disparities

- Given parallels to HIV PrEP to consider for doxy PEP, equitable implementation and delivery need to be prioritized

Gender disparities

- More doxy PEP efficacy trials that include cisgender women and people assigned female at birth regardless of gender are warranted

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Next steps for NYC Health Department

- Collect population-level measure of use (provider reporting)
- Education for, and collection of information on use among, patients and partners receiving case investigations and partner services
- Feedback from community members on experiences
- Surveys/qualitative assessments in Sexual Health Clinics
- Uptake and use patterns in Sexual Health Clinics

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

February 13, 2024 — The Health Department today released its 2022 Sexually Transmitted Infections (STIs) Surveillance Report highlighting the ongoing need for New Yorkers to get tested and treated for STIs and employ prevention tactics that work for them.

"Doxy PEP represents a significant advance in biomedical STI prevention. The tactical deployment of doxy PEP in populations disproportionately impacted by STIs is an important public health strategy with the potential to reverse years of increasing STI rates and to reduce the STI inequities that affect people of different ages, races and ethnicities, genders, and neighborhoods."

- Dr. Jason Zucker

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