Brigham and Women's Hospital
Founding Member, Mass General Brigham

Update on STIs, PrEP, and DoxyPEP

Kevin L. Ard, MD, MPH
Director, Sexual Health Clinic
Co-Clinical Director, Division of Infectious Diseases
Department of Medicine
Massachusetts General Hospital
Assistant Professor of Medicine
Harvard Medical School

Kevin L. Ard, MD, MPH

Washington University School of Medicine
Medicine Residency at Brigham & Women's Hospital
Infectious Disease Fellowship at BWH/MGH
Assistant Professor of Medicine, HMS
Director, Sexual Health Clinic, MGH
Co-Clinical Director, Division of Infectious Diseases, MGH

Clinical and research focus: Prevention and treatment of HIV and STIs

DISCLOSURES

In-kind research support from Binx Health
Royalties from McGraw-Hill and UpToDate
Research support from Gilead Sciences

OBJECTIVES

1. Describe recent updates in STI management and the evidence supporting the updates.

2. Summarize current options for HIV pre-exposure prophylaxis (PrEP).

3. Analyze the benefits and risks of doxycycline post-exposure prophylaxis (PEP) for STIs.

Sexually transmitted infections

1. POINT-OF-CARE TESTING FOR CHLAMYDIA, GONORRHEA, AND OTHER INFECTIONS
2. INCREASING CONCERNS ABOUT DRUG-RESISTANT GONORRHEA
3. CHALLENGES WITH *MYCOPLASMA GENITALIUM*

Expanding options for point-of-care diagnosis of chlamydia and gonorrhea

ADVANTAGES

- Permit accurate diagnosis and treatment in a single visit
- May impede transmission by shortening the period between testing and treatment
- May align with patient and clinician preferences

DISADVANTAGES OR QUESTIONS

- Some current platforms do not permit extragenital testing.
- Testing may take up to 90 minutes or longer, depending on the platform.
- The optimal management of symptomatic people who test negative is uncertain.
- Performance compared to “old fashioned” standards of care (e.g., Gram stain) is uncertain.

Case

An 18-year-old cisgender woman who has sex with cisgender men was found to have pharyngeal gonorrhea after one of her male partners was diagnosed with urethral gonorrhea.

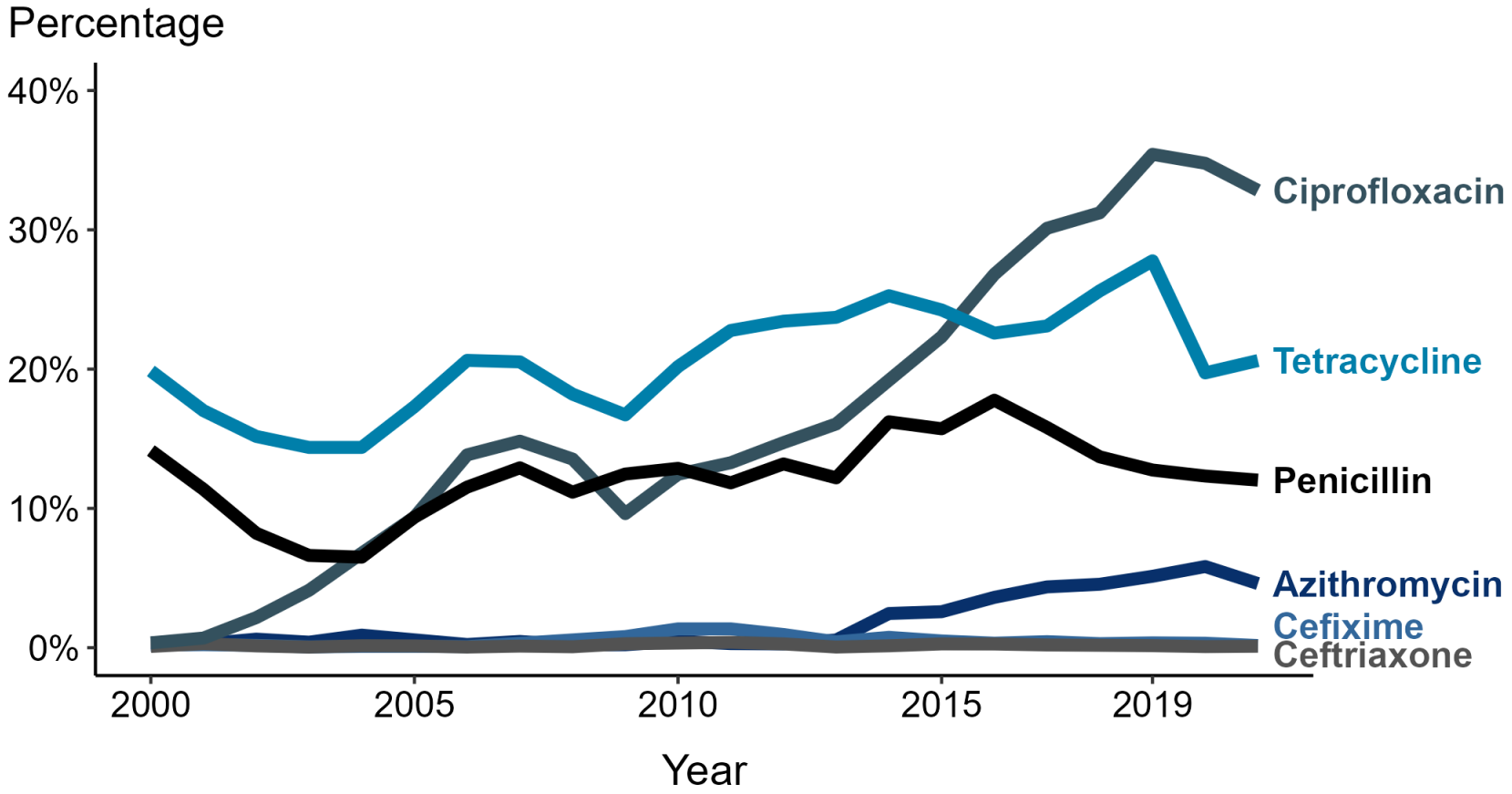
She received ceftriaxone 500 mg intramuscularly once.

She missed the appointment for a 2-week test of cure but returned at 5 weeks. She does not think she could have been re-exposed.

Repeat pharyngeal NAAT is positive for *N. gonorrhoeae*.

Is this re-infection or treatment failure, potentially due to drug resistance?

Neisseria gonorrhoeae — Prevalence of Tetracycline, Penicillin, or Ciprofloxacin Resistance* or Elevated Cefixime, Ceftriaxone, or Azithromycin Minimum Inhibitory Concentrations (MICs)†, by Year — Gonococcal Isolate Surveillance Project (GISP), 2000–2021



* Resistance: Ciprofloxacin: MIC ≥ 1.0 µg/mL; Penicillin: MIC ≥ 2.0 µg/mL or Beta-lactamase positive; Tetracycline: MIC ≥ 2.0 µg/mL

† Elevated MICs: Azithromycin: MIC ≥ 1.0 µg/mL 29 (2000–2004); ≥ 2.0 µg/mL (2005–2020); Ceftriaxone: MIC ≥ 0.125 µg/mL; Cefixime: MIC ≥ 0.25 µg/mL

NOTE: Cefixime susceptibility was not tested in 2007 and 2008.

The Commonwealth of Massachusetts
Executive Office of Health and Human Services
Department of Public Health
Bureau of Infectious Disease and Laboratory Sciences
305 South Street, Boston, MA 02130

MAURA T. HEALEY
Governor

KIMBERLEY DRISCOLL
Lieutenant Governor

Division of STD Prevention
Tel: (617) 983-6940
Fax: (617) 887-8790
www.mass.gov/dph/cdc/std

MARY A. BECKMAN
Acting Secretary

MARGRET R. COOKE
Commissioner

Tel: 617-624-6000
www.mass.gov/dph

CLINICAL ALERT

January 19, 2023

MULTI-DRUG NON-SUSCEPTIBLE GONORRHEA IN MASSACHUSETTS

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

- Enhanced surveillance has identified a second isolate that, based on its genome, likely has similarly reduced susceptibility to ceftriaxone and cefixime.

RAPID COMMUNICATION

Detection of 10 cases of ceftriaxone-resistant *Neisseria gonorrhoeae* in the United Kingdom, December 2021 to June 2022

Michaela Day[1], Rachel Pitt[1], Nisha Mody[1], John Saunders[1], Rupa Rai[1], Achyuta Nori[1], Hannah Church[1], Sarah Mensforth[1], Helen Corkin[1], Jacqueline Jones[2], Preneshni Naicker[3], Wazirzada M Khan[1], Rebecca Thomson Glover[1], Kalani Mortimer[1], Chloe Hylton[1], Elizabeth Moss[1], Thomas Joshua Pasvol[1], Ania Richardson[1], Suzy Sun[1], Neil Woodford[1], Hamish Mohammed[1], Katy Sinka[1], Helen Fifer[1]

1. National Incident Management Team, United Kingdom Health Security Agency, London, United Kingdom
2. Sexual Health Department Singleton Hospital, Swansea Bay University Health Board, Swansea, Wales, United Kingdom*
3. Public Health Wales Microbiology Swansea, Singleton Hospital, Swansea, Wales, United Kingdom*

Correspondence: Helen Fifer (helen.fifer@ukhsa.gov.uk)

In China, the proportion of ceftriaxone-resistant *N. gonorrhoeae* isolates increased from 2.9% in 2017 to 8.1% in 2022.

Steps if gonococcal treatment failure is suspected

1. Elicit a sexual history to assess for the possibility of re-infection.
2. Perform gonococcal culture in addition to NAAT at all exposed sites.
3. Select a treatment, noting that most cases of suspected treatment failure are re-infections.
4. Report the possibility of treatment failure to the local public health department.

Case

A 37-year-old cisgender man presents with 3 days of dysuria and urethral discharge.

In the past 3 months, he has had insertive and receptive anal sex with 3 men, using condoms about half the time.

Physical examination shows scant, mucoid urethral discharge.

Gonorrhea/chlamydia NAAT from the urine is **negative**.

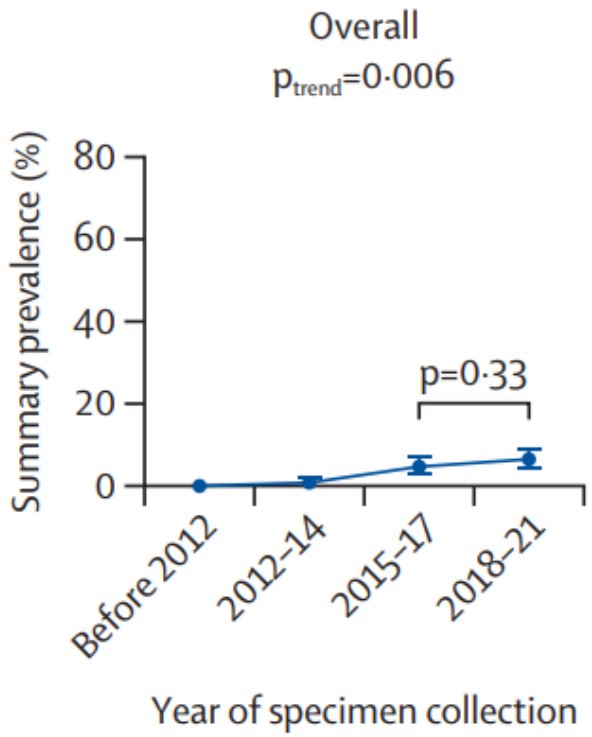
He is treated with doxycycline 100 mg by mouth twice daily for 7 days.

His symptoms improve but increase 5 days after stopping doxycycline.

A urine NAAT for *Mycoplasma genitalium* is **positive**.

Mycoplasma genitalium is increasingly problematic.

- Urogenital infection is present in 17% of sexual health clinic attendees, including 27% of men with urethritis.
- Urogenital co-infection occurs in 28% of chlamydia and 24% of gonorrhea cases.
- Macrolide resistance is present in 51-71% of infections in the US.
- Macrolide resistance testing is available through at least one commercial laboratory.
- Fluoroquinolone resistance is present in 13% of infections worldwide.



Dual-class resistance in *M. genitalium*

Manhard LE, Clin Infect Dis, 2023; www.labcorp.com/tests/180092/mycoplasma-genitalium-naa-swab-with-reflex-to-macrolide-resistance-testing; Teck-Phui C, Lancet Microbe, 2024

Mycoplasma genitalium – Key points

When to Test

- Recurrent NGU or cervicitis
- Consider testing in pelvic inflammatory disease
- Asymptomatic screening **not recommended**

How to Test

- FDA approved genital and urine NAAT

Treatment

- Doxycycline followed by moxifloxacin
- Sex partners of symptomatic persons treated **only if positive**

Slide courtesy of Jason Zucker, MD, MS

Treatment of *M. genitalium*

Recommended Regimens if *M. genitalium* Resistance Testing is Available

If *macrolide sensitive:* **Doxycycline** 100 mg orally 2 times/day for 7 days, followed by **azithromycin** 1 g orally initial dose, followed by 500 mg orally once daily for 3 additional days (2.5 g total)

If macrolide resistant: Doxycycline 100 mg orally 2 times/day for 7 days followed by **moxifloxacin** 400 mg orally once daily for 7 days

Recommended Regimens if *M. genitalium* Resistance Testing is Not Available

If *M. genitalium* is detected by an FDA-cleared NAAT: Doxycycline 100 mg orally 2 times/day for 7 days, followed by **moxifloxacin** 400 mg orally once daily for 7 days

www.cdc.gov/std/treatment-guidelines/default.htm

Case, continued

He takes moxifloxacin once daily for 7 days.

His symptoms improve slightly but never resolve; one week after completing treatment, his symptoms worsen again.

He has not had sex since beginning doxycycline.

A repeat urine NAAT for *Mycoplasma genitalium* is **positive**.

Options for management of *M. genitalium* treatment failure are limited.

Regimen	Proportion cured
Pristinamycin for 10 days (+/- doxycycline)	75%-100% (not available in the U.S.)
Minocycline for 14 days	68%-71%
Minocycline + metronidazole for 14 days	81%
Tinidazole for 7 days	(successful case report)

Bissesor M, Clin Infect Dis, 2015; Doyl M, Open Forum Infect Dis, 2020; Read TRH, Emerg Infect Dis, 2018; Clarke EJ, Open Forum Infect Dis, 2023; Htaik K, J Antimicrob Chemother, 2025; Liscynesky C, Sex Transm Dis, 2025

M. genitalium might be associated with preterm birth.

Systematic review and meta-analysis of pregnancy outcomes associated with *M. genitalium*

- 10 studies with small sample sizes (N = 137-1338)
- **Preterm birth:** Adjusted OR (95% CI) = **2.34 (1.17, 4.71)**
- **Spontaneous abortion:** Adjusted OR (95% CI) = **1.00 (0.53, 1.89)**

Frenzer C, Sex Transm Infect, 2022

PrEP for HIV

Case

A 27-year-old cisgender woman presents requesting PrEP.

She is overweight (BMI 29.4) but has no other chronic medical problems and takes no medications.

She has had condomless vaginal sex with two cisgender men in the past 6 months.

Three months ago, she was treated for secondary syphilis.

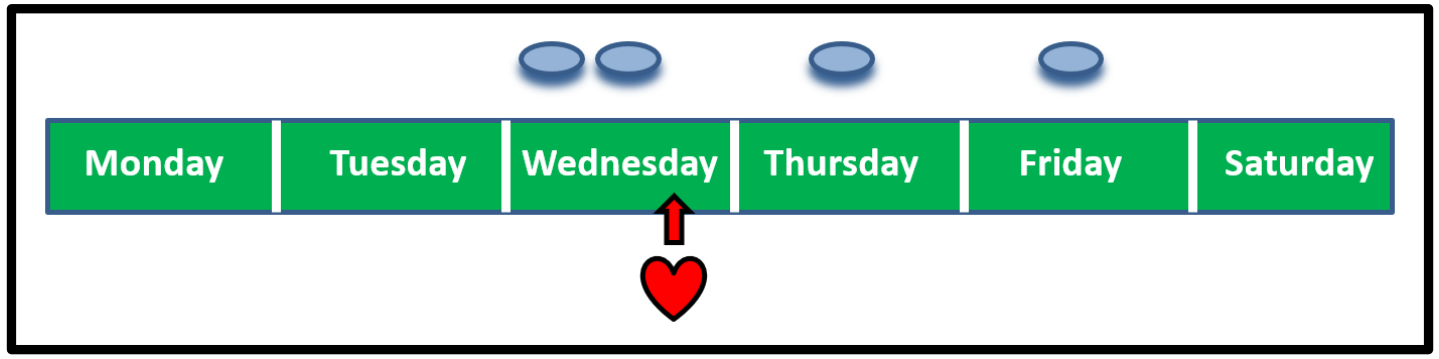
TDF/FTC

- **Evidence:** Prevents HIV acquisition through sex and injection drug use; efficacy has been demonstrated among men who have sex with men (MSM), transgender women, and cisgender heterosexual men and women
- **Dosing:** One tablet (emtricitabine [FTC] 200 mg and tenofovir disoproxil fumarate [TDF] 300 mg) once daily*
- **Advantages:**
  - Longest clinical experience among PrEP agents, including in pregnancy
  - Available as a generic
  - Can be used in an on-demand fashion by MSM*
- **Disadvantages:**
  - Renal toxicity and decreased bone mineral density
  - Requires baseline hepatitis B testing

Centers for Disease Control and Prevention: US Public Health Service: Preexposure prophylaxis for the prevention of HIV infection in the United States – 2021 update: a clinical practice guideline. 2021.

On-demand TDF/FTC (“2-1-1”)

- Considered an alternative for MSM without chronic hepatitis B
- With TDF/FTC only; no published data with other PrEP agents
- On-demand TDF/FTC is associated with more GI side effects than daily dosing
- Follow the same laboratory monitoring strategy as for daily oral TDF/FTC



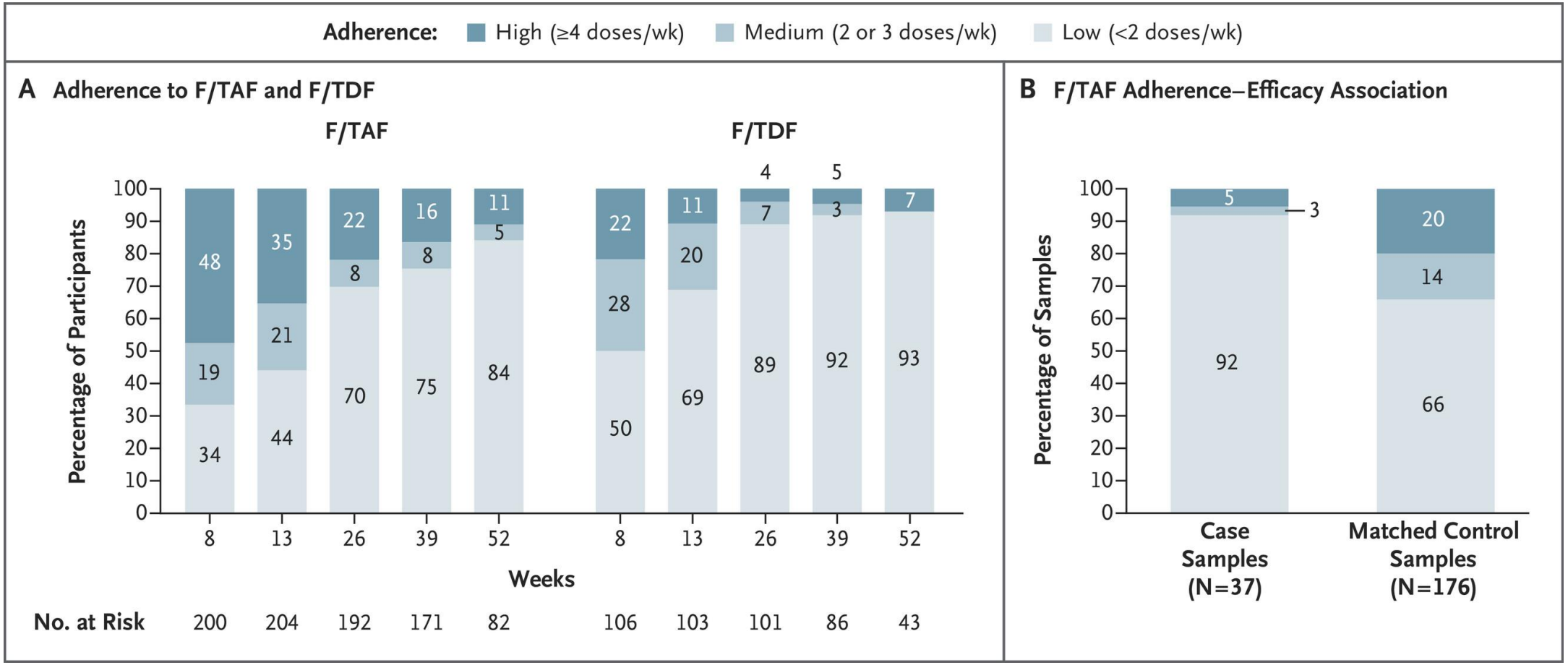
Centers for Disease Control and Prevention: US Public Health Service: Preexposure prophylaxis for the prevention of HIV infection in the United States – 2021 update: a clinical practice guideline. 2021. Molina JM, CROI 2026

TAF/FTC

- **Evidence:** Prevents HIV acquisition through sex; non-inferior to TDF/FTC among men who have sex with men (MSM) and transgender women
- **Dosing:** One tablet (emtricitabine [FTC] 200 mg and tenofovir alafenamide [TAF] 25 mg) once daily
- **Advantages:**
  - Fewer renal and bone effects in comparison to TDF/FTC
- **Disadvantages:**
  - Evidence for benefit among people whose HIV risk arises from receptive vaginal sex limited, though the IAS-USA now recommends TAF/FTC for women if TDF/FTC is contraindicated or undesirable
  - Has mild deleterious effects on lipids and weight
  - Requires baseline hepatitis B testing

Centers for Disease Control and Prevention: US Public Health Service: Preexposure prophylaxis for the prevention of HIV infection in the United States – 2021 update: a clinical practice guideline. 2021. Landovitz RJ, JAMA, 2025

TAF/FTC prevents HIV among women with high adherence.



Bekker LG, N Engl J Med, 2024

Cabotegravir (CAB)

- **Evidence:** Prevents HIV acquisition through sex; superior to TDF/FTC for PrEP among MSM, transgender women, and cisgender heterosexual women
- **Dosing:**
  - Cabotegravir 600 mg intramuscularly once monthly for 2 doses, then every 2 months
  - An oral lead-in phase of cabotegravir 30 mg once daily prior to the first injection is optional.
- **Advantages:**
  - Obviates the need for daily pill adherence
  - Superior to TDF/FTC for PrEP in a range of populations
- **Disadvantages:**
  - Injection site reactions are common, although often mild.
  - Benefits navigation may be time-consuming.
  - Same-day initiation may not be possible currently.
  - Implications of the medication's tail phase
  - If HIV occurs despite CAB, HIV test interpretation may be challenging.

Landovitz RJ, N Engl J Med, 2021; Delany-Moretlwe S, Lancet, 2022

Lenacapavir (LEN)

- **Evidence:** Prevents HIV acquisition through sex among cisgender men and women and transgender and gender diverse people
- **Dosing:**
  - Lenacapavir 927 mg subcutaneously every 26 weeks (+/- 2 weeks)
  - Lenacapavir 600 mg by mouth daily for 2 days with initiation of the drug
- **Advantages:**
  - Infrequent dosing interval
  - Superior to TDF/FTC for PrEP in a range of populations
  - Can be used in pregnancy
- **Disadvantages:**
  - Injection site reactions are common, although often mild.
  - Benefits navigation may be time-consuming.
  - Same-day initiation may not be possible currently.
  - Implications of the medication's tail phase
  - Drug-drug interactions

Bekker LG, N Engl J Med, 2024; Kelley CF, N Engl J Med, 2025

Considerations for selecting a PrEP agent with a patient

What do they prefer?	Comorbidities	Nature of HIV exposure	Logistics
Which PrEP agent do they want, and why?	Renal or bone disease favors TAF/FTC or CAB	Limited efficacy data for TAF/FTC among cisgender women	A desire for telehealth/limited in-person visits favors oral PrEP
	Hepatitis B favors oral PrEP	TDF is the only agent studied among people who inject drugs	On-demand dosing favors TDF/FTC
	Hyperlipidemia, weight concerns favor TDF/FTC or CAB		Same-day initiation favors oral PrEP
			Insurance considerations may favor a specific agent

DoxyPEP

Randomized trials of doxycycline post-exposure prophylaxis (PEP)

In all, participants in the intervention arm were to take doxycycline 200 mg once within 72 hours after sex.

Study	Population	Primary Endpoint	Results
Substudy of IPERGAY	232 MSM on PrEP	Occurrence of 1st STI (GC, CT, syphilis)	HR 0.53 (0.33-0.85) overall
DoxyPEP	501 MSM and TGW with HIV or on PrEP	Incidence of at least one STI per quarter	HR for PrEP and HIV cohorts 0.34 (0.23-0.51) and 0.48 (0.28-0.83), respectively
DOXYVAC	502 MSM on PrEP	Time to first episode of syphilis or CT	aHR 0.16 (0.08-0.30) overall
dPEP	449 cisgender women on PrEP	Incidence of GC, CT, syphilis	RR 0.88 (0.60-1.29)

Potential harms of doxycycline PEP

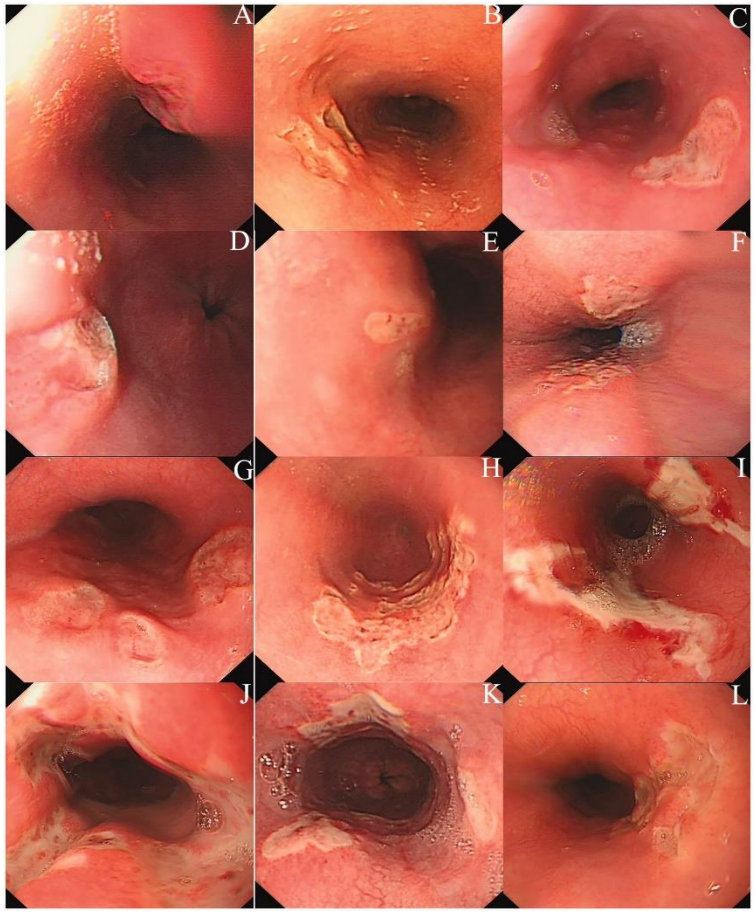
Known medication side effects

- Gastrointestinal, dermatologic
- Serious adverse events were not more common with doxycycline in trials of doxycycline PEP.

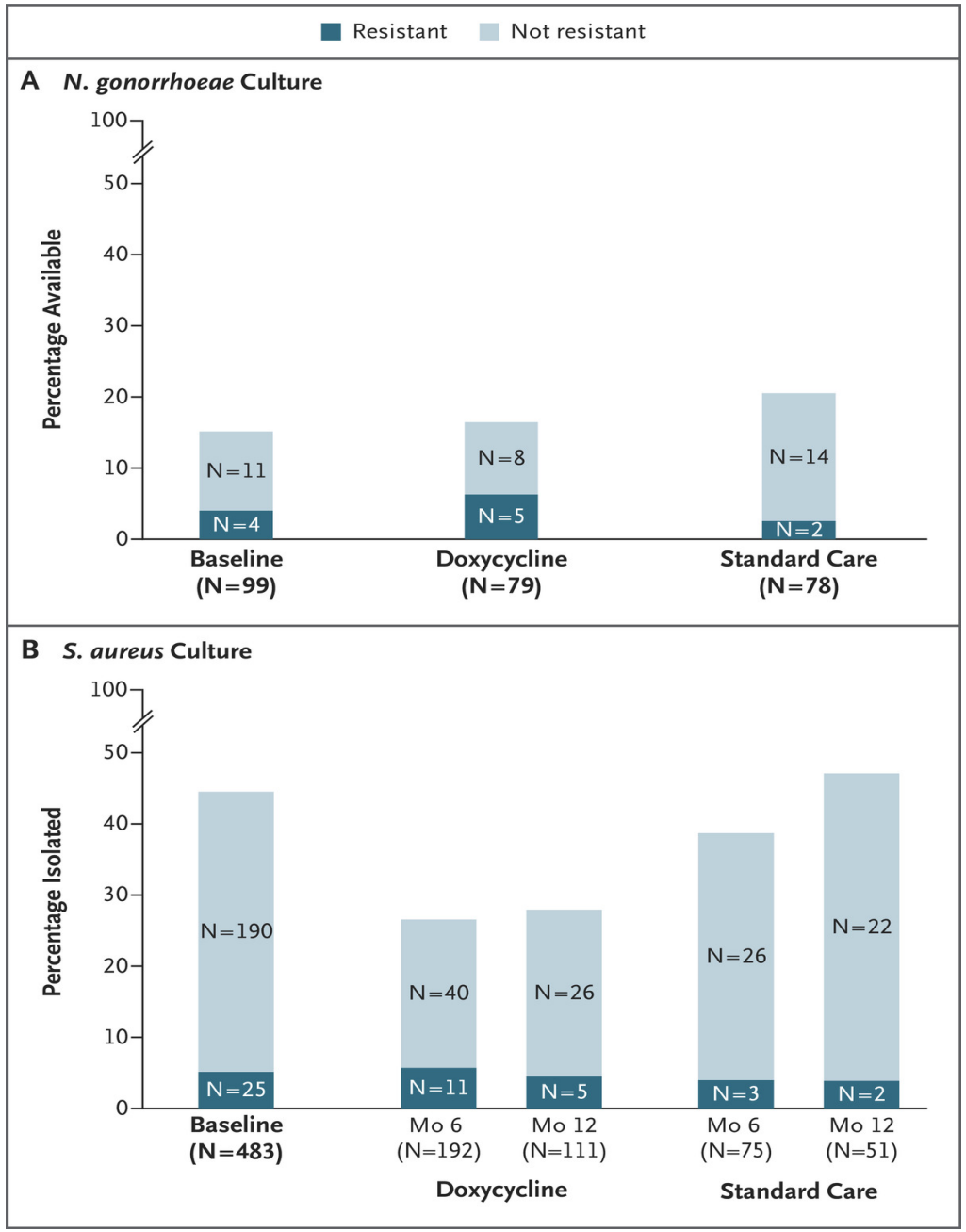
Antimicrobial resistance

Effects on the microbiome

Impaired diagnosis of syphilis?



Tetracycline and doxycycline resistance in the DoxyPEP study – a mixed picture



Luetkemeyer AF, N Engl J Med, 2023

How will doxycycline PEP impact the microbiome?

- Microbiome perturbations are associated with obesity and other chronic diseases.
- How to counsel patients about microbiome changes is uncertain.
- Comparing microbiomes of people who received doxycycline PEP versus intermittent doxycycline, ceftriaxone, penicillin, etc.
- Doxycycline is one of the least *C. difficile*-promoting antibacterials.

Cox LM, Nat Rev Endocrinol, 2015; Desphande A, J Antimicrob Chemother, 2013

CDC doxy PEP recommendations

BOX 1. CDC recommendations for use of doxycycline as postexposure prophylaxis for bacterial sexually transmitted infections prevention

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.

Bachmann LA, MMWR Recomm Rep, 2024

Take-Home Points

- There are expanding options for point-of-care diagnosis of chlamydia and gonorrhea, but gaps remain.
- Most suspected gonococcal treatment failures are re-infections, but antimicrobial resistance is of increasing concern.
- The optimal approach to *M. genitalium* treatment failure is not known. Minocycline is the most readily available option.
- Selection of agents for HIV PrEP hinges upon patient preference, comorbidities, the nature of HIV exposure, and logistical considerations.
- Consider doxycycline post-exposure prophylaxis for MSM and transgender women with recent STIs.

References

Workowski KA, et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep. 2021;70(4):1-192.

Gandhi RT, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2022 recommendations of the International Antiviral Society-USA Panel. *JAMA*. 2024; doi:10.1001/jama.2024.24543.