Brigham and Women's Hospital
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Update on STIs, PrEP, and DoxyPEP

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

DISCLOSURES

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OBJECTIVES

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

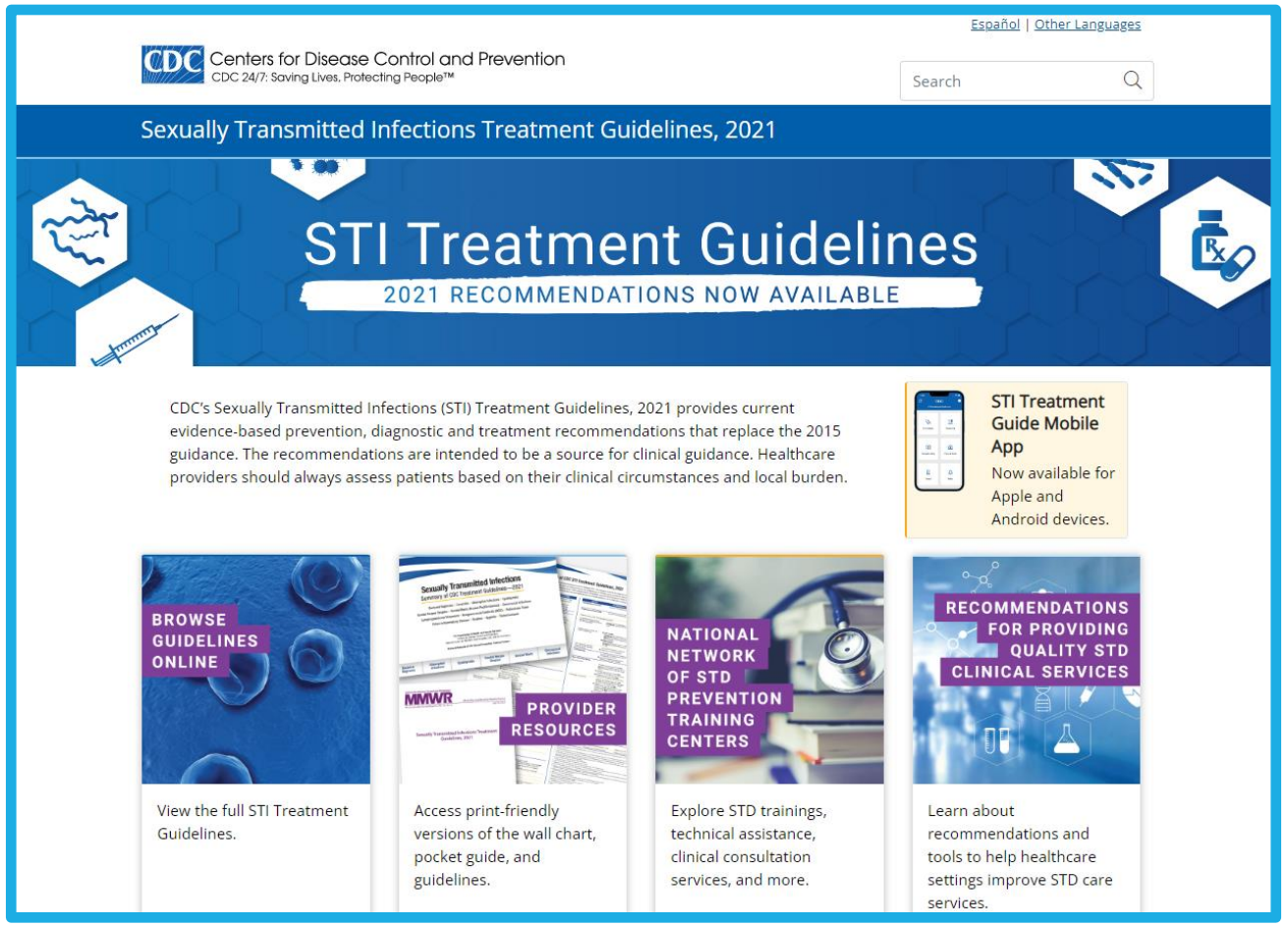
2. Summarize current options for HIV pre-exposure prophylaxis (PrEP).

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*

CDC's 2021 STI Treatment Guidelines



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

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.

Van der Pol B, JAMA Netw Open, 2020; Dawkins M, Sex Transm Dis, 2022

Case

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

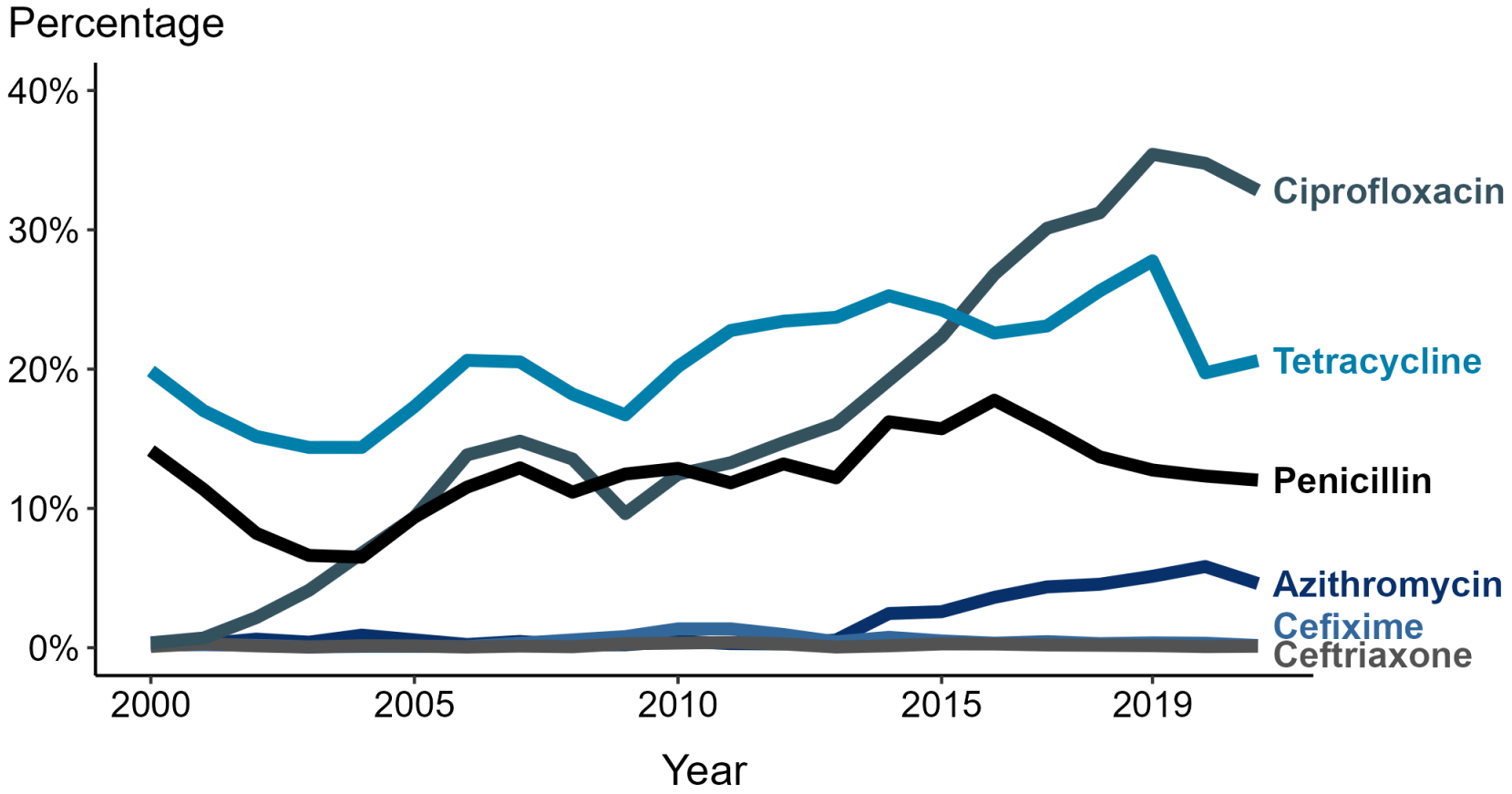
She received ceftriaxone 500 mg intramuscularly once.

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.

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CLINICAL ALERT

January 19, 2023

MULTI-DRUG NON-SUSCEPTIBLE GONORRHEA IN MASSACHUSETTS

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

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

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]

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

Michaela D, Euro Surveill, 2022; Zhu X, MMWR Morb Mortal Wkly Rep, 2024

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 – Key points

When to Test

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

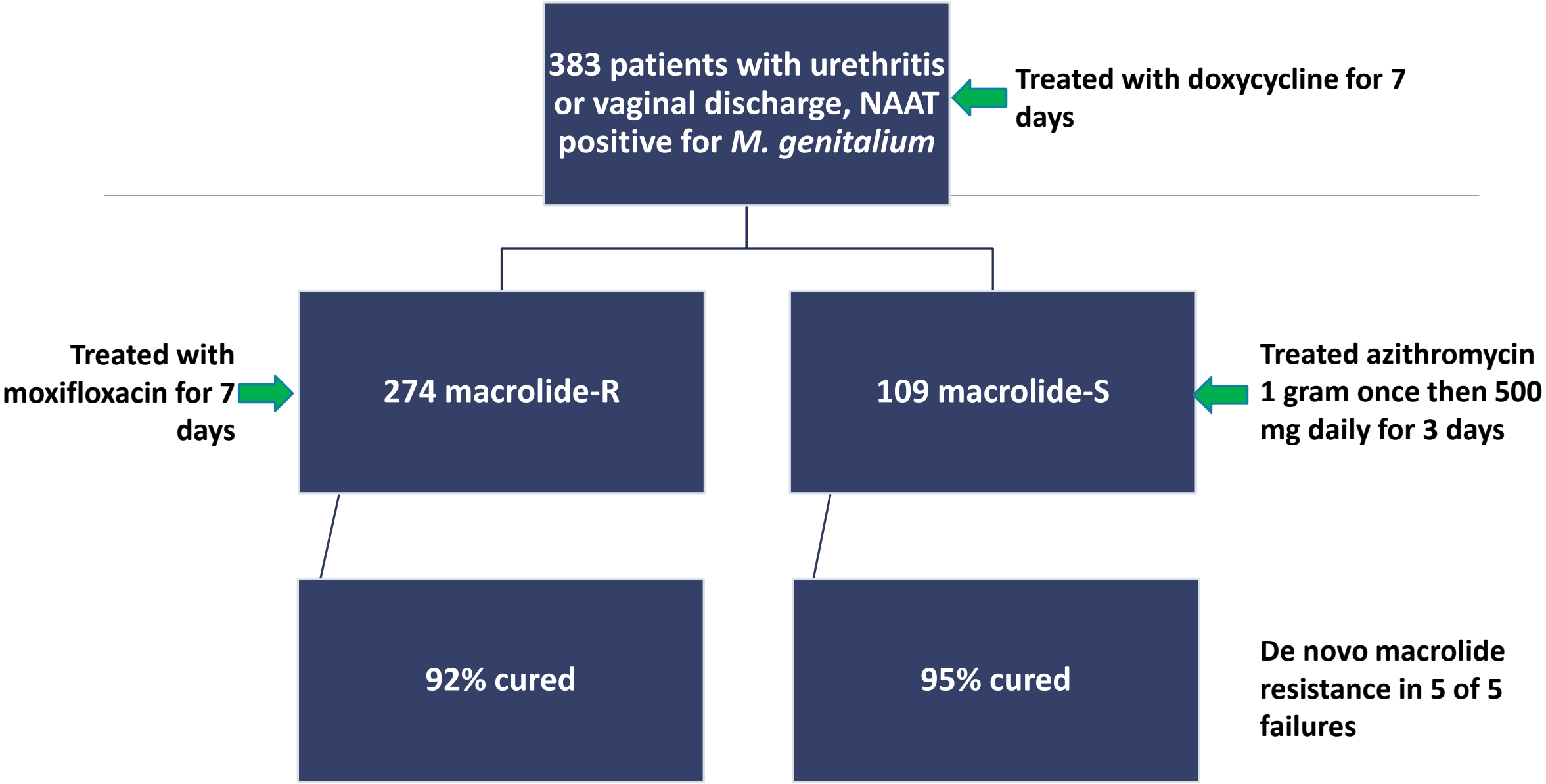
How to Test

- 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



Durukan D, Clin Infect Dis, 2020

Treatment of *M. genitalium*

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

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

Case, continued

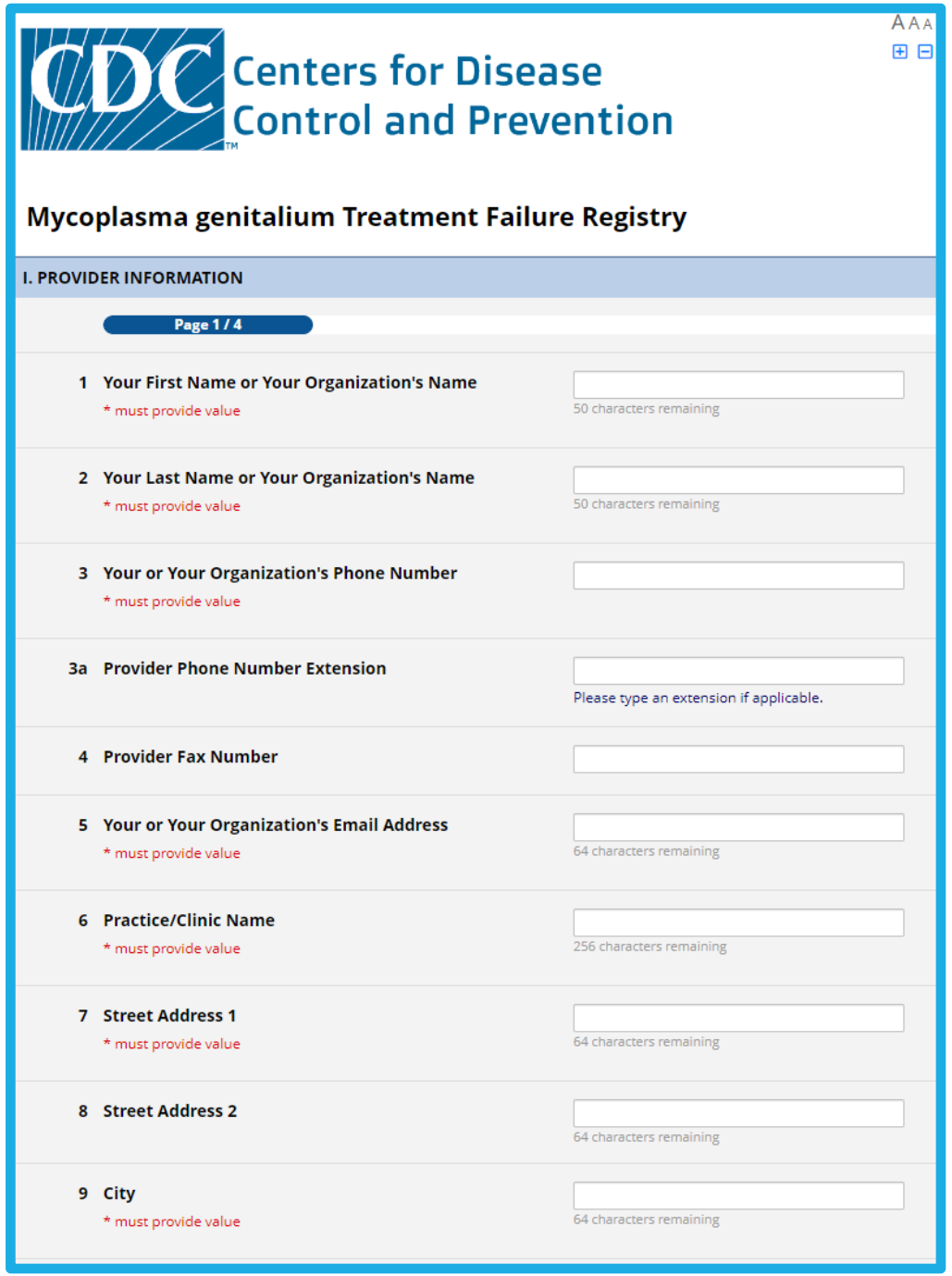
He takes moxifloxacin once daily for 7 days.

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**.

M. genitalium treatment failure registry



Centers for Disease Control and Prevention

Mycoplasma genitalium Treatment Failure Registry

I. PROVIDER INFORMATION

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1 **Your First Name or Your Organization's Name**
* must provide value
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2 **Your Last Name or Your Organization's Name**
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3 **Your or Your Organization's Phone Number**
* must provide value

3a **Provider Phone Number Extension**
Please type an extension if applicable.

4 **Provider Fax Number**

5 **Your or Your Organization's Email Address**
* must provide value
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6 **Practice/Clinic Name**
* must provide value
256 characters remaining

7 **Street Address 1**
* must provide value
64 characters remaining

8 **Street Address 2**
64 characters remaining

9 **City**
* must provide value
64 characters remaining

https://airc.cdc.gov/surveys/index.php?s=7NCDV

Options for *M. genitalium* treatment failure

Based on expert opinion and assuming drug susceptibility testing is not available and reinfection is unlikely:

Minocycline

Doxycycline + pristinamycin (compassionate use only)

Doxycycline + sitafloxacin (compassionate use only)

M. genitalium might be associated with preterm birth.

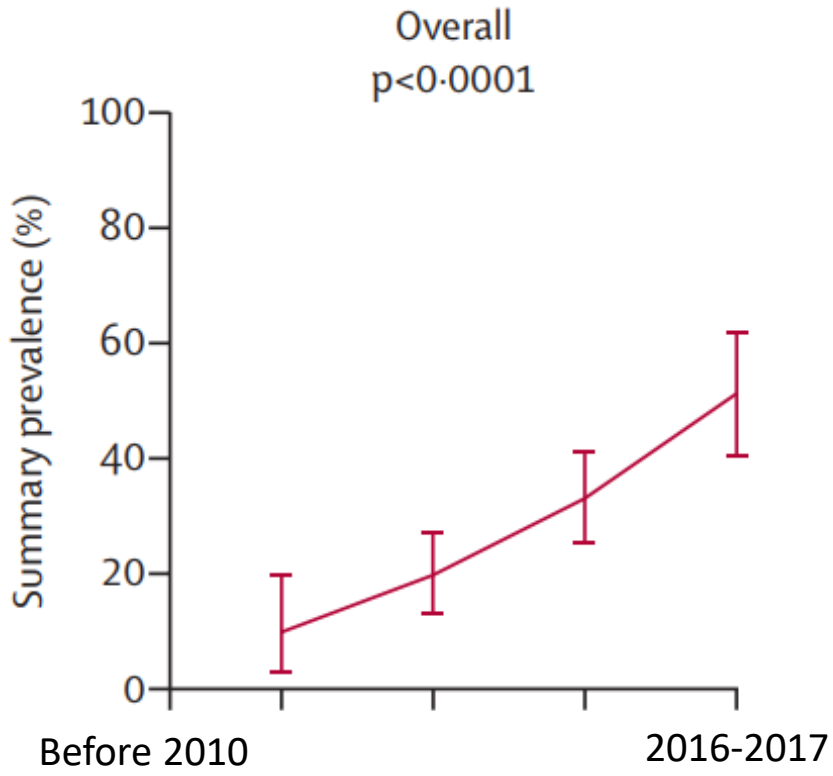
Systematic review and meta-analysis of pregnancy outcomes associated with *M. genitalium*

- 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)**

An approach in pregnancy: Extended-duration azithromycin

- **Azithromycin 1 gram, then 500 mg daily for 4 days**
- But, macrolide resistant mutations are increasingly common in *M. genitalium*.
- Azithromycin fails to cure 87% of people with macrolide resistant infections.

Worldwide prevalence of macrolide resistance in *M. genitalium*



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.

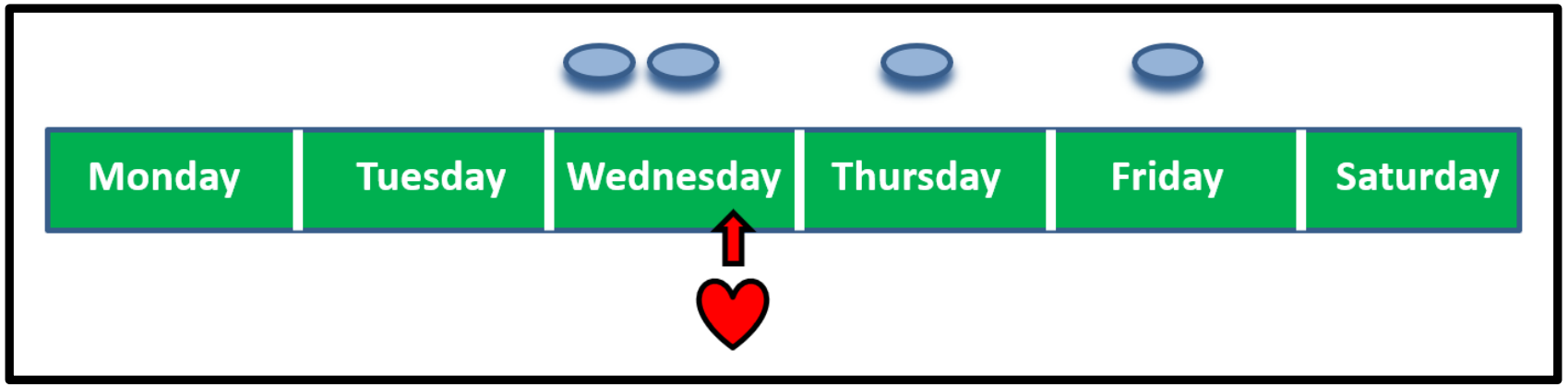
Three months ago, she was treated for secondary syphilis.

TDF/FTC (Tenofovir disoproxil fumarate/emtricitabine)

- **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
  - Baseline hepatitis B testing is recommended

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
- Prescribe no more than 30 tablets at a time before retesting for HIV
- Follow the same laboratory monitoring strategy as for daily oral TDF/FTC



TAF/FTC (Tenofovir alafenamide/emtricitabine)

- **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:**
  - Efficacy for people whose HIV risk arises from receptive vaginal sex is unknown
  - Has mild deleterious effects on lipids and weight
  - Baseline hepatitis B testing is recommended

CAB (Long-acting injectable cabotegravir)

- **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.

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

Case

- A 19-year-old cisgender man presents on-time for his 3rd injection of cabotegravir. He feels well and has no symptoms. One month ago, he had condomless anal sex with a cisgender man with HIV who is virologically suppressed.
- Prior to initiation of cabotegravir, he had a negative HIV RNA and antibody/antigen test.
- At the time of his second injection, an HIV RNA assay and antibody/antigen test were negative.
- Today, he receives his injection and has blood drawn for routine monitoring. The results include:
  - HIV antibody/antigen test: Negative
  - HIV RNA assay: **Detected but < 20 copies/mL**

Managing ambiguous HIV test results for people taking PrEP

1. Ask about medication adherence since the last test
2. Repeat blood testing for HIV antibody/antigen and HIV RNA after a few days
3. Manage antiretrovirals while repeating testing:

Strategy	Pros	Cons
Continue PrEP	For adherent patients, ambiguous results are likely false positives; provides ongoing protection against HIV	Risk of HIV drug resistance if truly infected
Add a third antiretroviral	Provides a fully suppressive treatment regimen	HIV test results may remain ambiguous if truly infected
Stop PrEP for 1-2 weeks	Facilitates clarification of HIV status	Removes PrEP's protection if HIV-uninfected

Preexposure prophylaxis for the prevention of HIV infection in the United States – 2021 update. CDC. 2021.

Is this a false positive test or a breakthrough HIV infection?

- CDC guidelines recommend HIV RNA assays for PrEP monitoring, but how to adjudicate ambiguous results is not clear.
- In rare cases of breakthrough infection on cabotegravir, assay reversion was common.
- Some quantitative HIV RNA assays are not FDA-approved for diagnosis but a qualitative assay is.

Assay Reversion

	Days since 1st HIV pos visit	Rapid test	Ag/Ab test	Qualitative RNA test (LLOD 30 c/mL)	Confirmatory Ab test	Viral load (LLOQ 40 c/mL or single copy)	DNA test (LLOD 4.09 c/10^6 cells)
11 months	0	NR	NR	R		6.1	
	42	NR	NR	NR			
	55	NR	NR	R		ND	
	98	NR	NR	NR			
	105	R	R	NR	NEG		Detect <LLOD
	112	NR	R	NR	NEG		
	119	NR	NR	NR			
	132	NR	R	NR	INDET		ND
	195	R	NR	NR			Detect <LLOD
	235	NR	R	NR	INDET		
	280	NR	R	R	NEG	<40	Detect 5.8
	333	R	R	R	INDET	<40	

Eshleman, CROI 2023, Abstract 160

Acute HIV versus the LEVI syndrome

Feature	Acute HIV	LEVI syndrome
Viral replication	Explosive	Smoldering
Symptoms	Fever, chills, malaise, lymphadenopathy	Minimal, often absent
Detection	HIV RNA assays, antigen/antibody tests	Often low/undetectable RNA, diminished/delayed antibody production
Assay reversion	Rare	Common
Duration	1-2 weeks	Months
Transmission	Likely	Unlikely
Drug resistance	No, unless transmitted	Yes, even when the viral load is low

LEVI = Long acting early viral inhibition syndrome

HIV RNA tests are no longer recommended for monitoring on PrEP.

Laboratory Testing

- At initiation or after a long hiatus, HIV screening should include an HIV RNA test and a laboratory-based antigen-antibody test (evidence rating: AIIa).
    - If RNA testing is unavailable, initiation of PrEP after a rapid HIV antibody test and while awaiting a laboratory-based antigen/antibody test result is recommended (evidence rating: BIII).
- For long-acting cabotegravir PrEP follow-up, a rapid HIV antibody test and laboratory-based antigen/antibody test, not routine RNA testing, is recommended (evidence rating: AIIb).
- If RNA testing is not available, repeat antigen/antibody testing 1 month after starting or resuming tenofovir-based oral PrEP (evidence rating: AIII).

Gandhi RT, JAMA, 2024

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

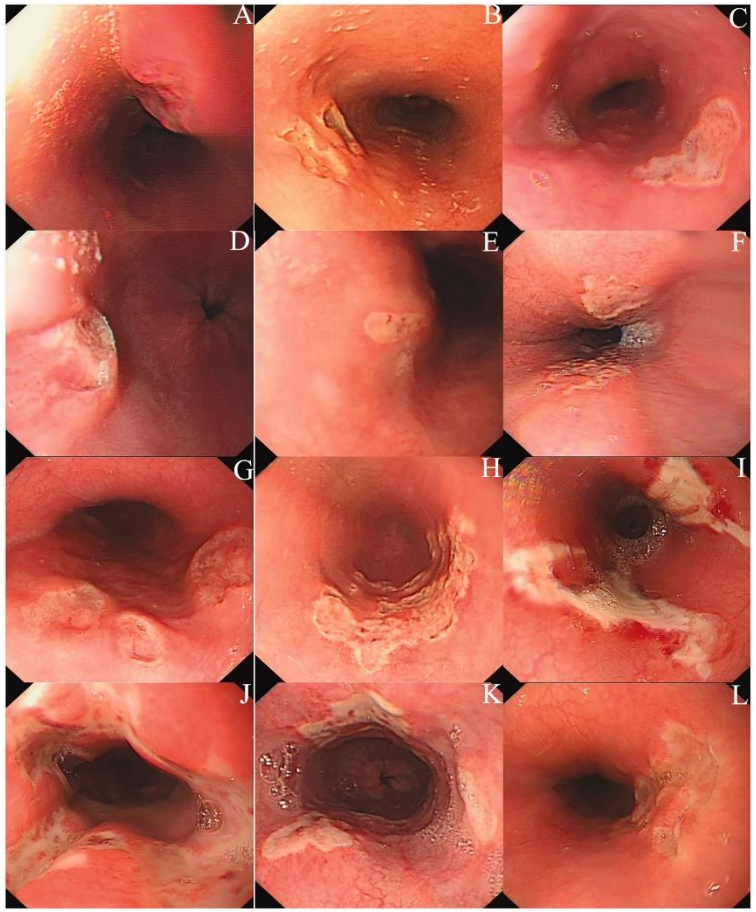
Known medication side effects

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

Antimicrobial resistance

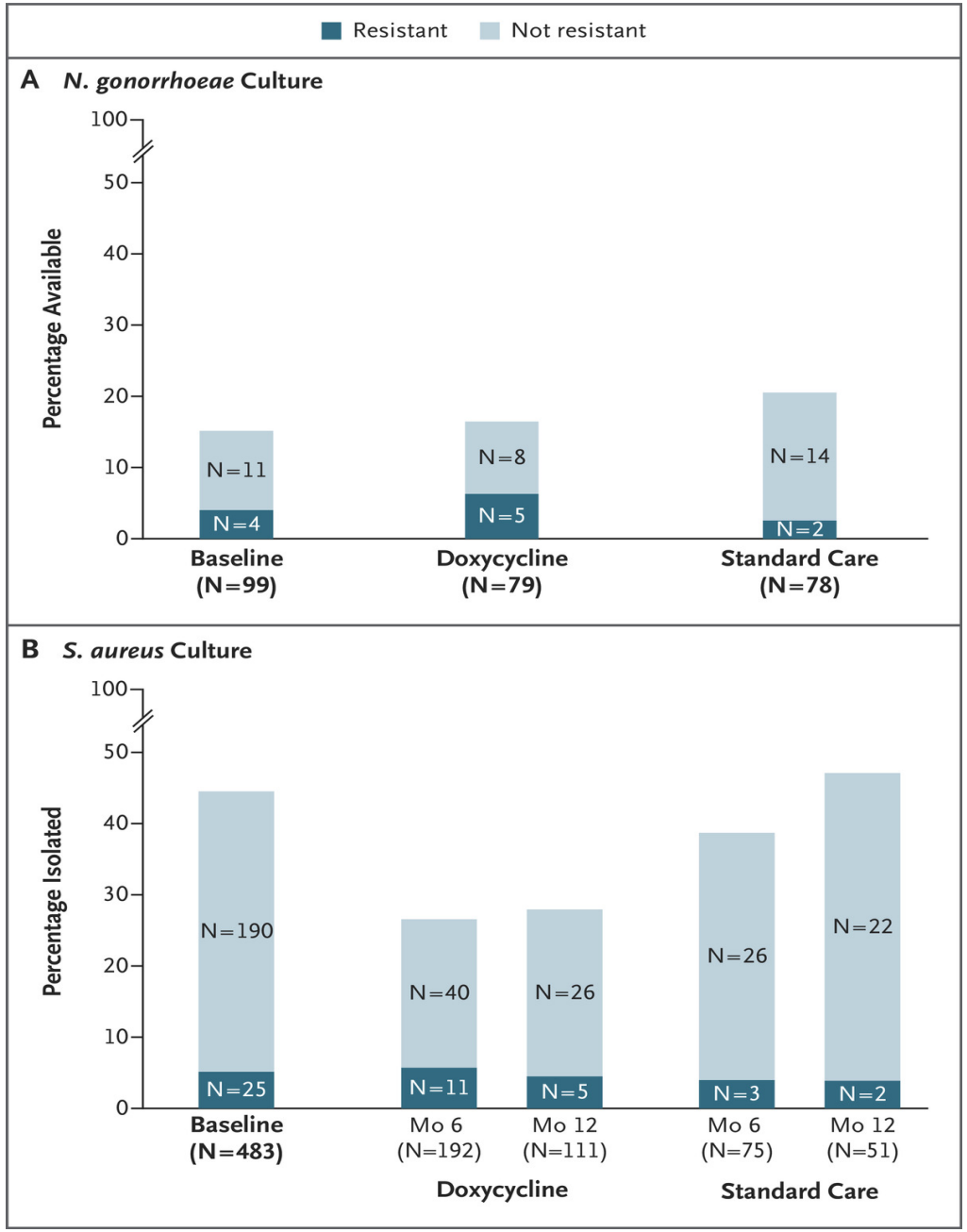
Effects on the microbiome

Impaired diagnosis of syphilis?



Luetkemeyer AF, N Engl J Med, 2023; Molina JM, Lancet Infect Dis, 2019; Molina JM, CROI, 2023; Guo Y, J Int Med Res, 2019; Kong FYS, J Antimicrob Chemother,2023

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.
- HIV RNA testing is no longer recommending for monitoring on PrEP.
- 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.