

STD Update 2019: New Realities, Treatment Recommendations, and Clinical Controversies

What's New in Medicine, 2019 – 9/6/19

Julie Dombrowski, MD, MPH
Associate Professor of Medicine, University of Washington
Deputy Director, HIV/STD Program
Public Health – Seattle & King County

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- Received grant research support from Hologic

Learning Objectives

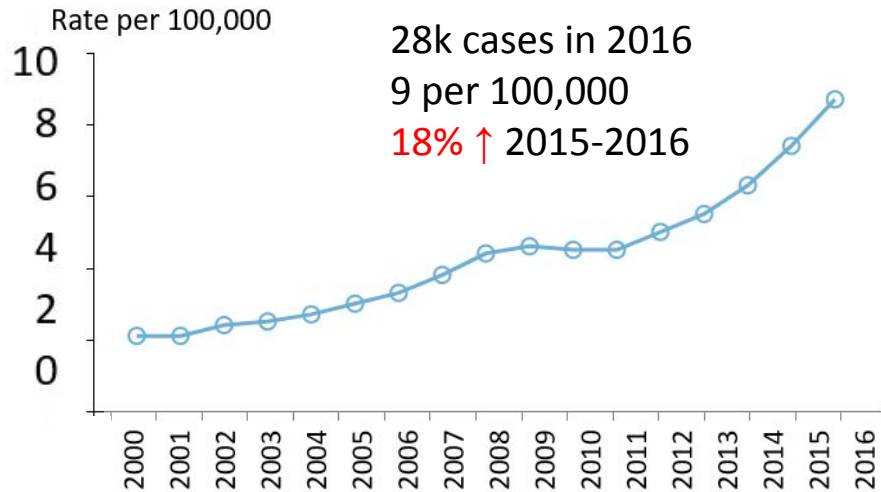
- Know the epidemiology of STIs common in the Northwest
- Know the current key points about diagnosis, treatment and prevention of STIs
- Interpret and understand tests to detect STIs

Outline

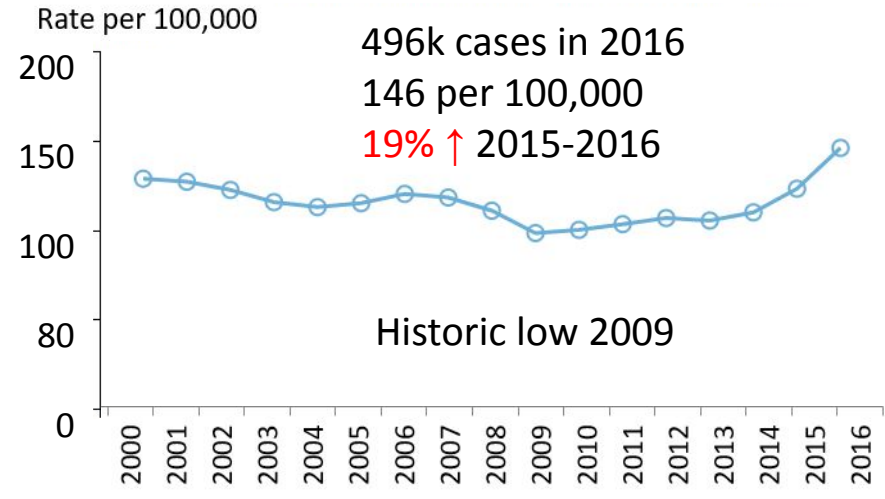
- Epidemiology update
- 5 things all HIV clinicians should be doing
- 3 clinical controversies
- What's coming next

Bacterial STI Rates, U.S., 2000-2016

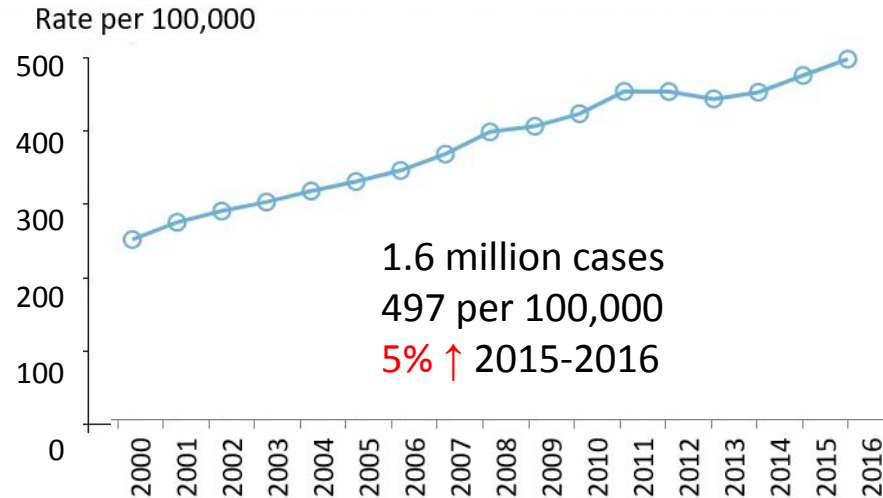
Syphilis



Gonorrhea



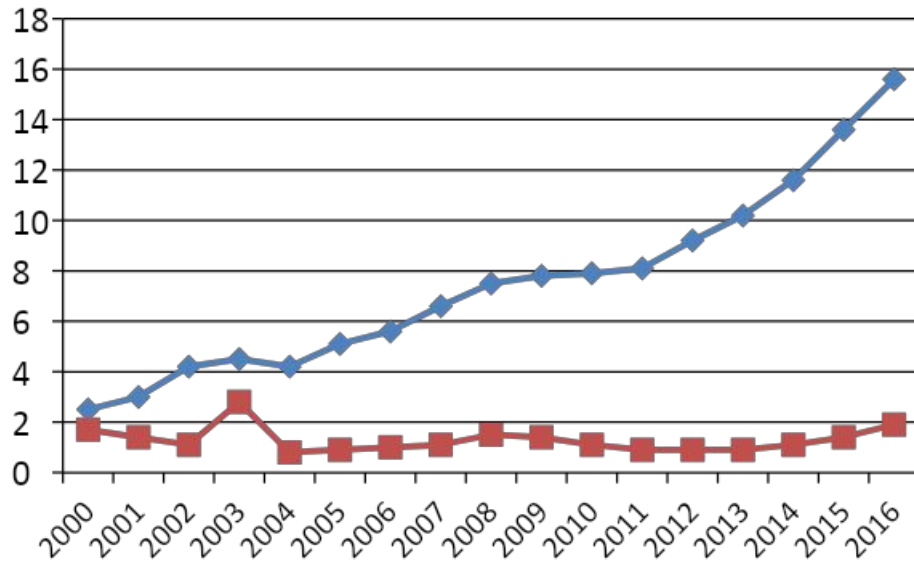
Chlamydia



STI Rates by Sex, U.S., 2000-2016

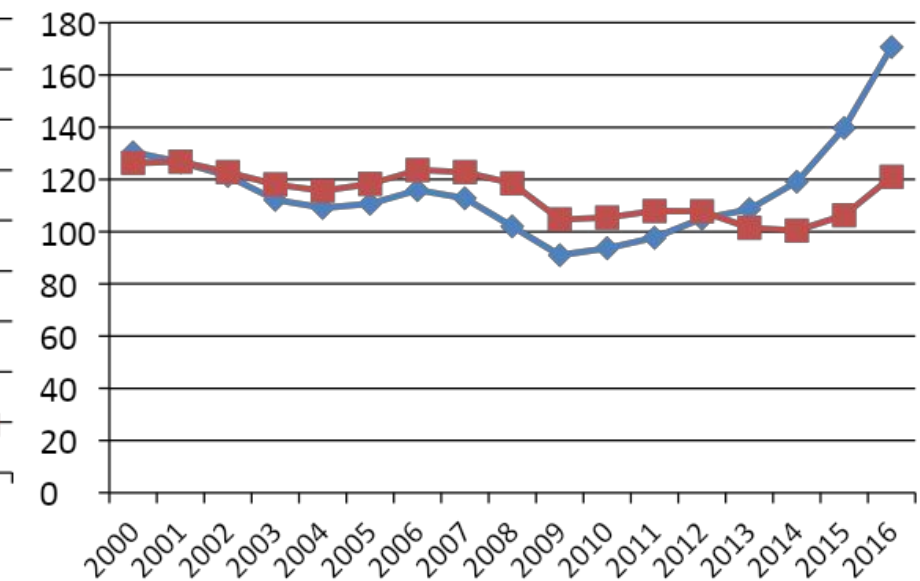
Syphilis

Rate per 100,000



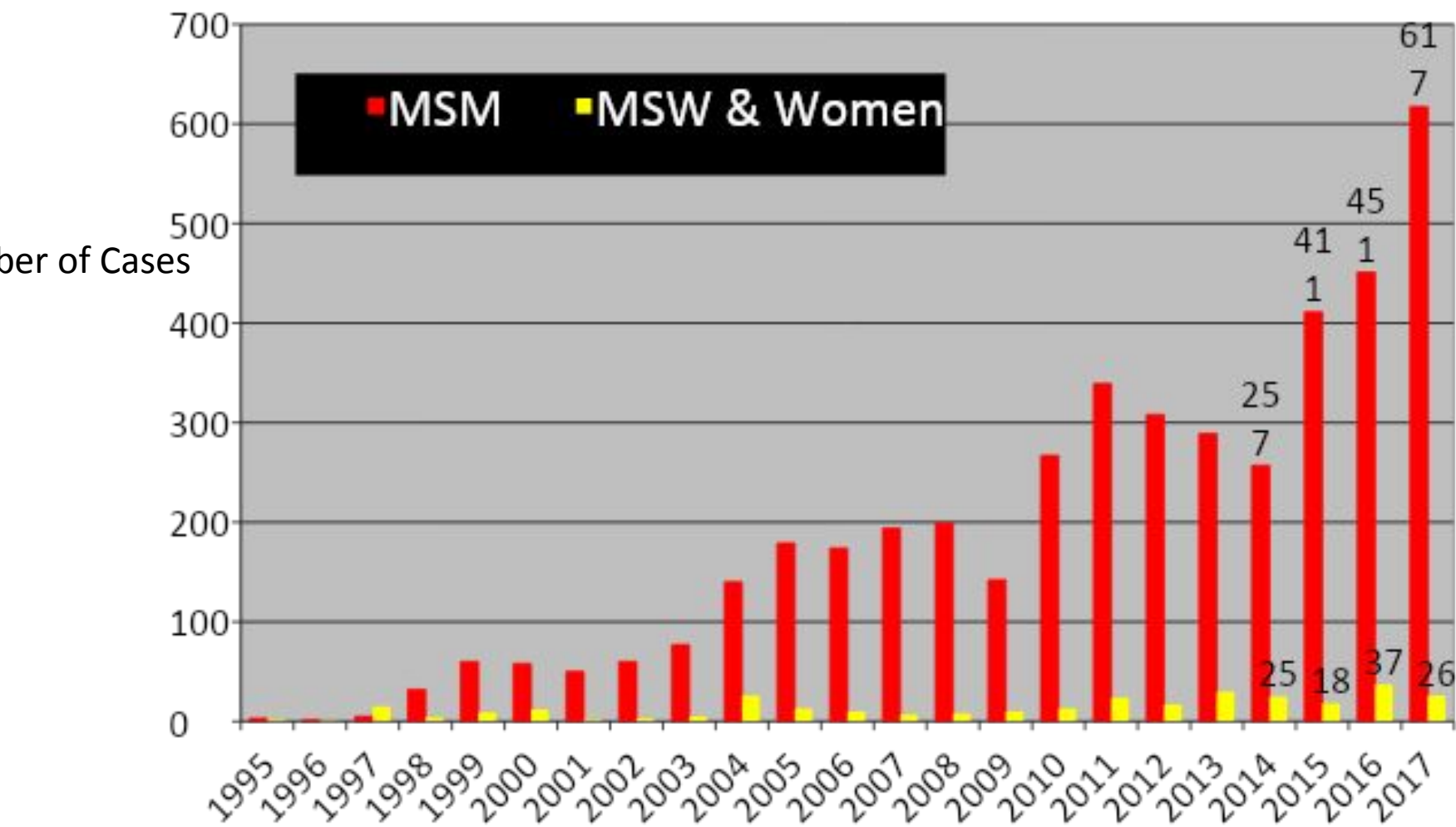
Gonorrhea

Rate per 100,000

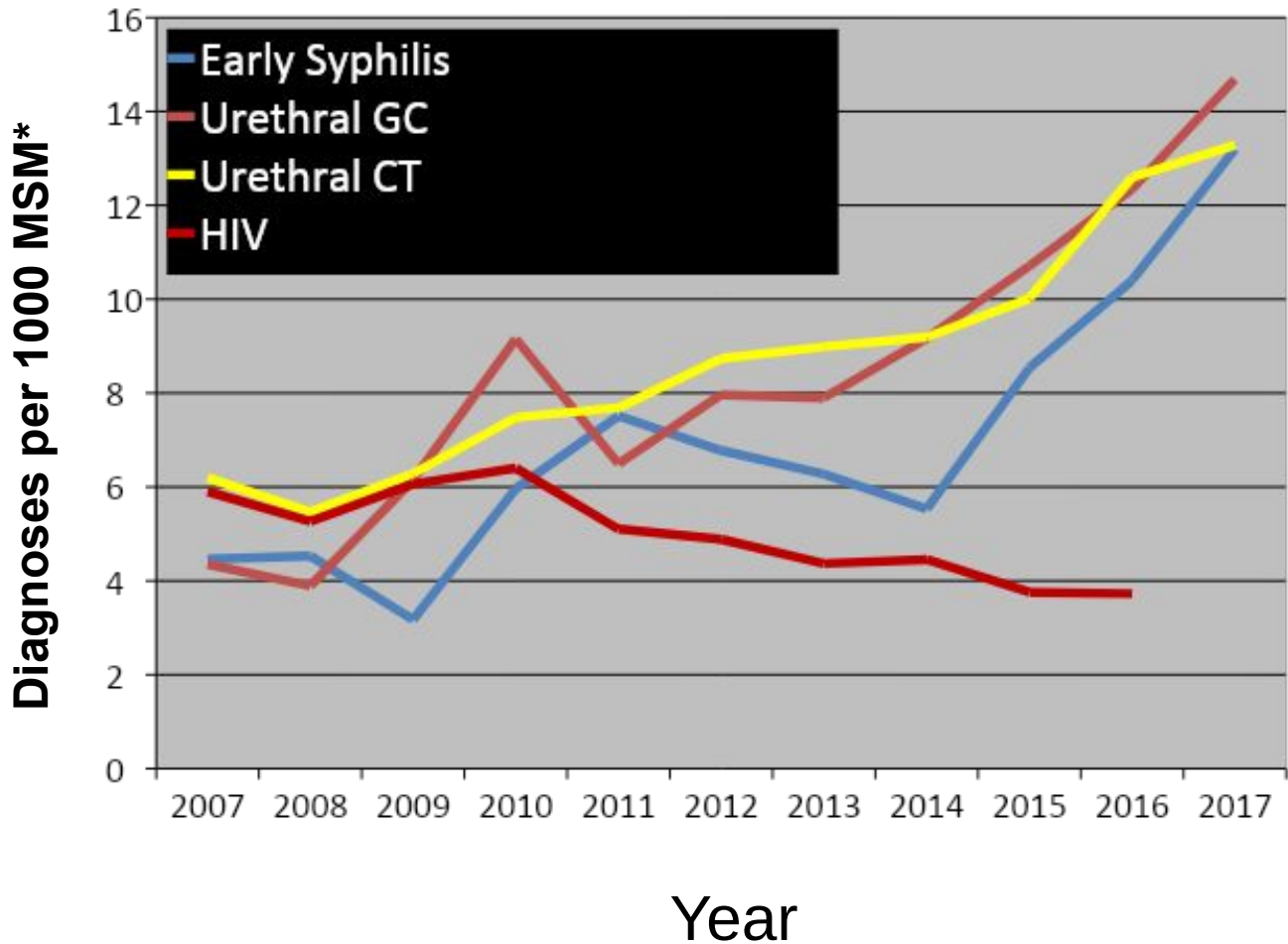


- ◆— Male
- Female

Early Syphilis in King County 1994-2017, by Gender/Sexual Orientation



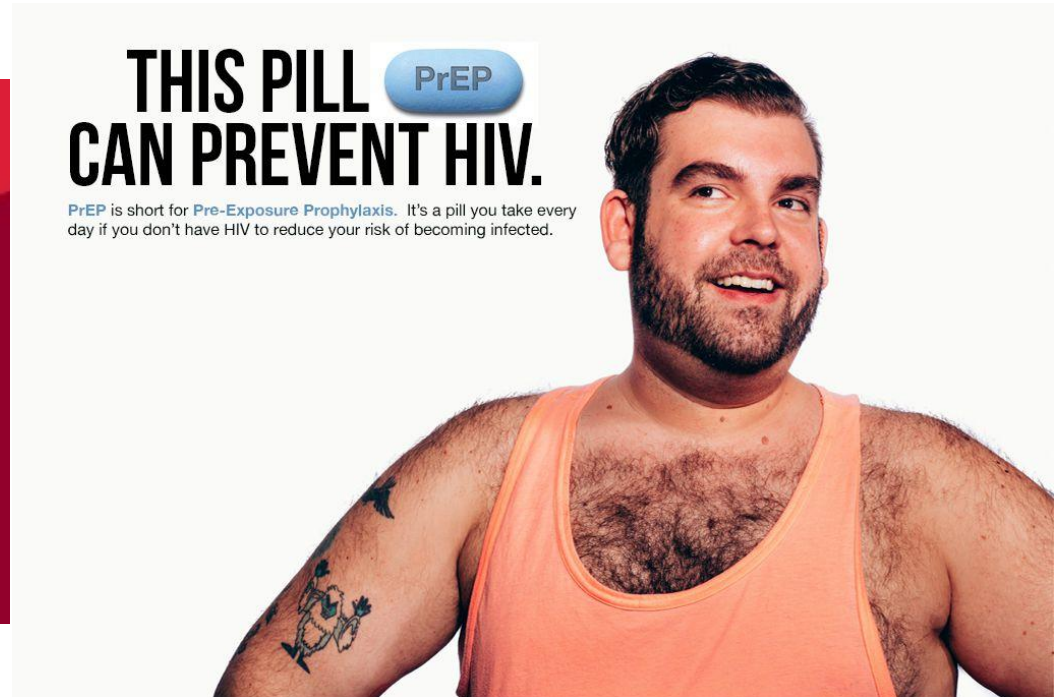
Incidence of Bacterial STIs and HIV among MSM in King County, WA 2007-2017



STI	Trend
Syphilis	↑195%
Urethral GC	↑237%
Urethral CT	↑114%
HIV	↓37%

* Assumes 5.7% men are MSM

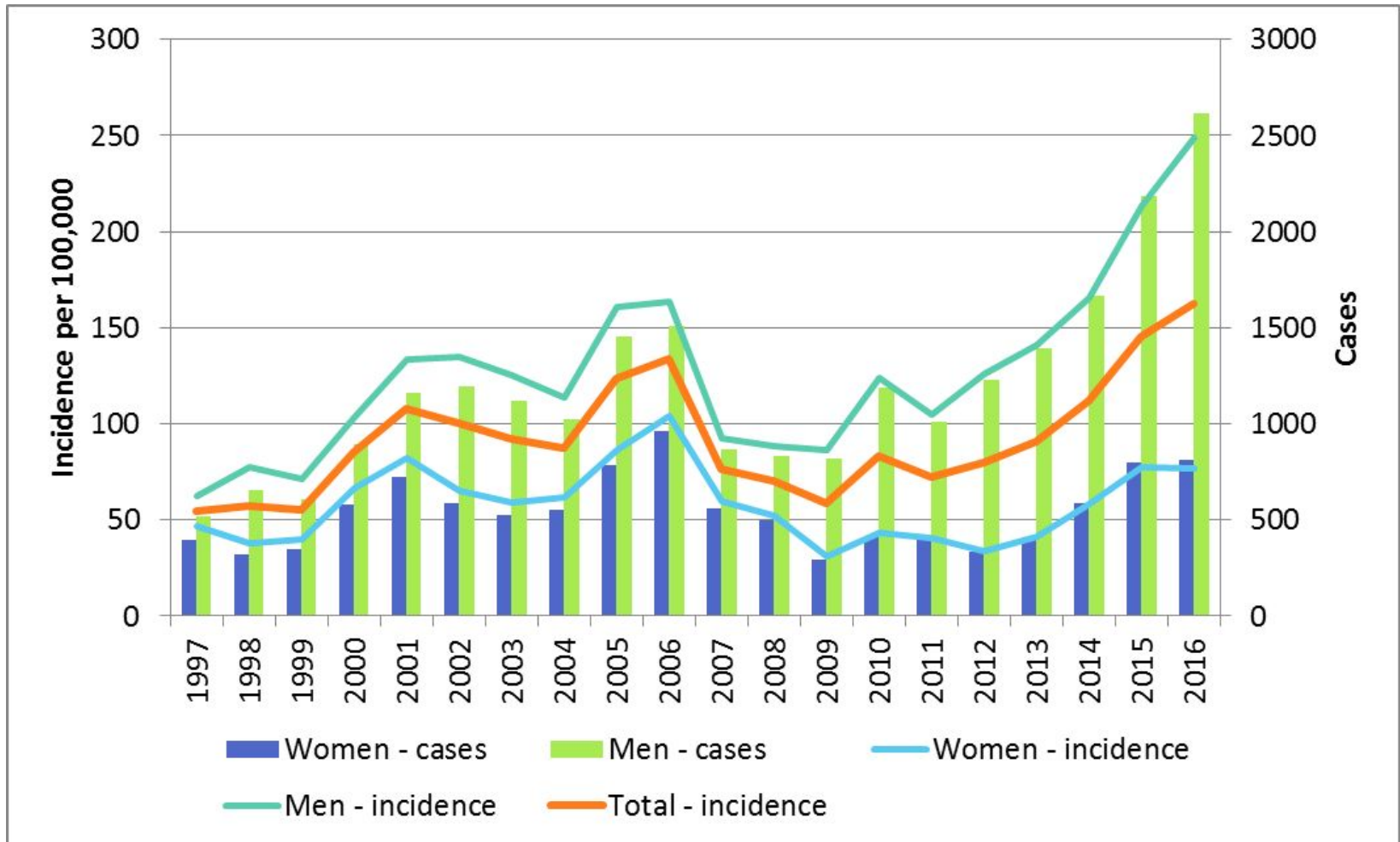
Rising STI rates among MSM: A public health problem arising from a public health success



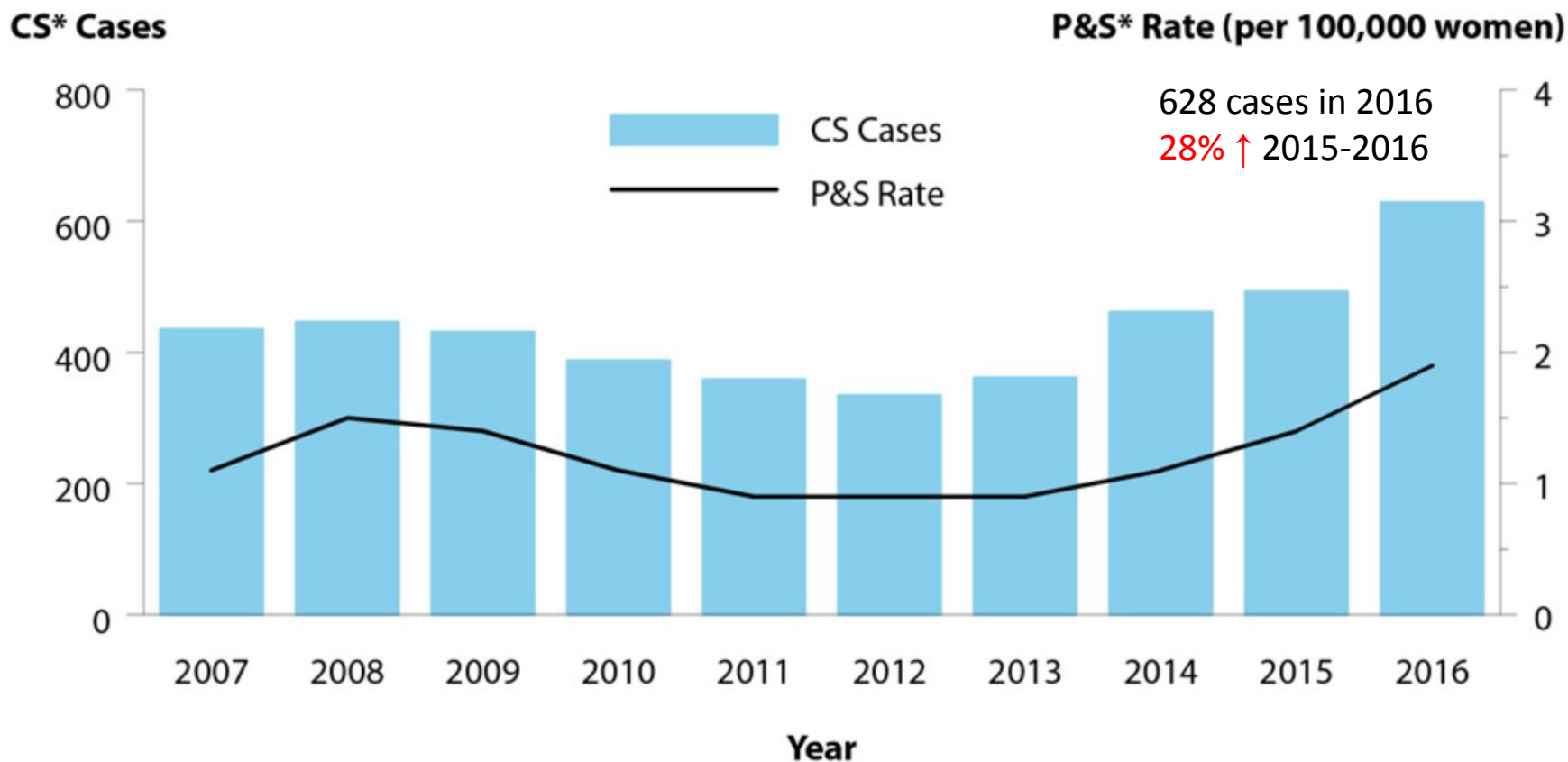
Decoupling of HIV & STD Prevention

STI Rates Also Increasing in Women

Gonorrhea Cases and Incidence, by sex, King County, WA, 1997-2016

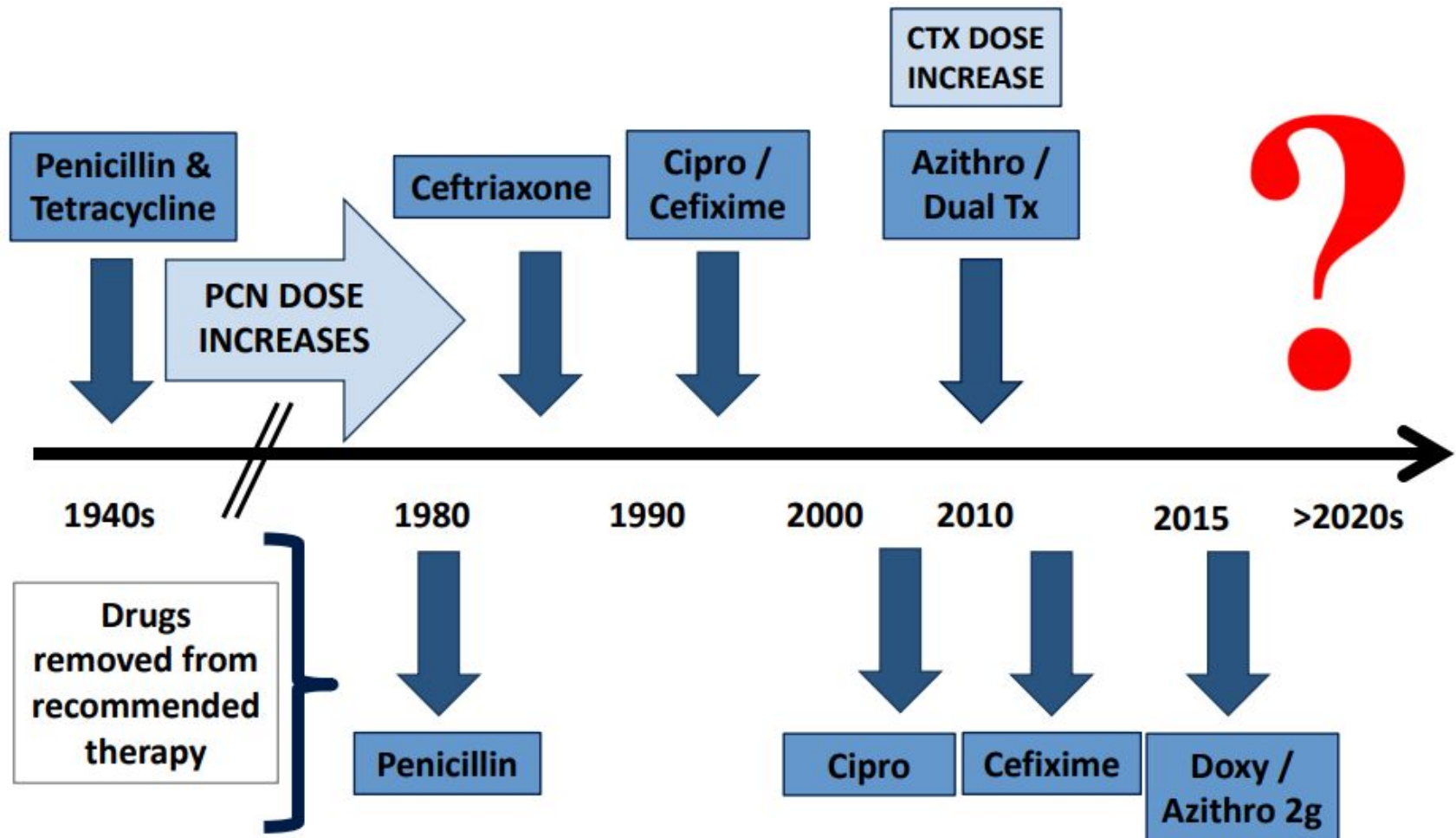


Congenital Syphilis Cases and Primary and Secondary Syphilis Rates in Women, U.S. 2007-2016



Gonorrhea Treatment Threatened by Decreased Antimicrobial Susceptibility

Historical Timeline of Recommended Treatment for Gonorrhea



Decreased susceptibility to azithromycin among isolates at the Public Health – Seattle & King County STD Clinic by year: 2012 – 2016

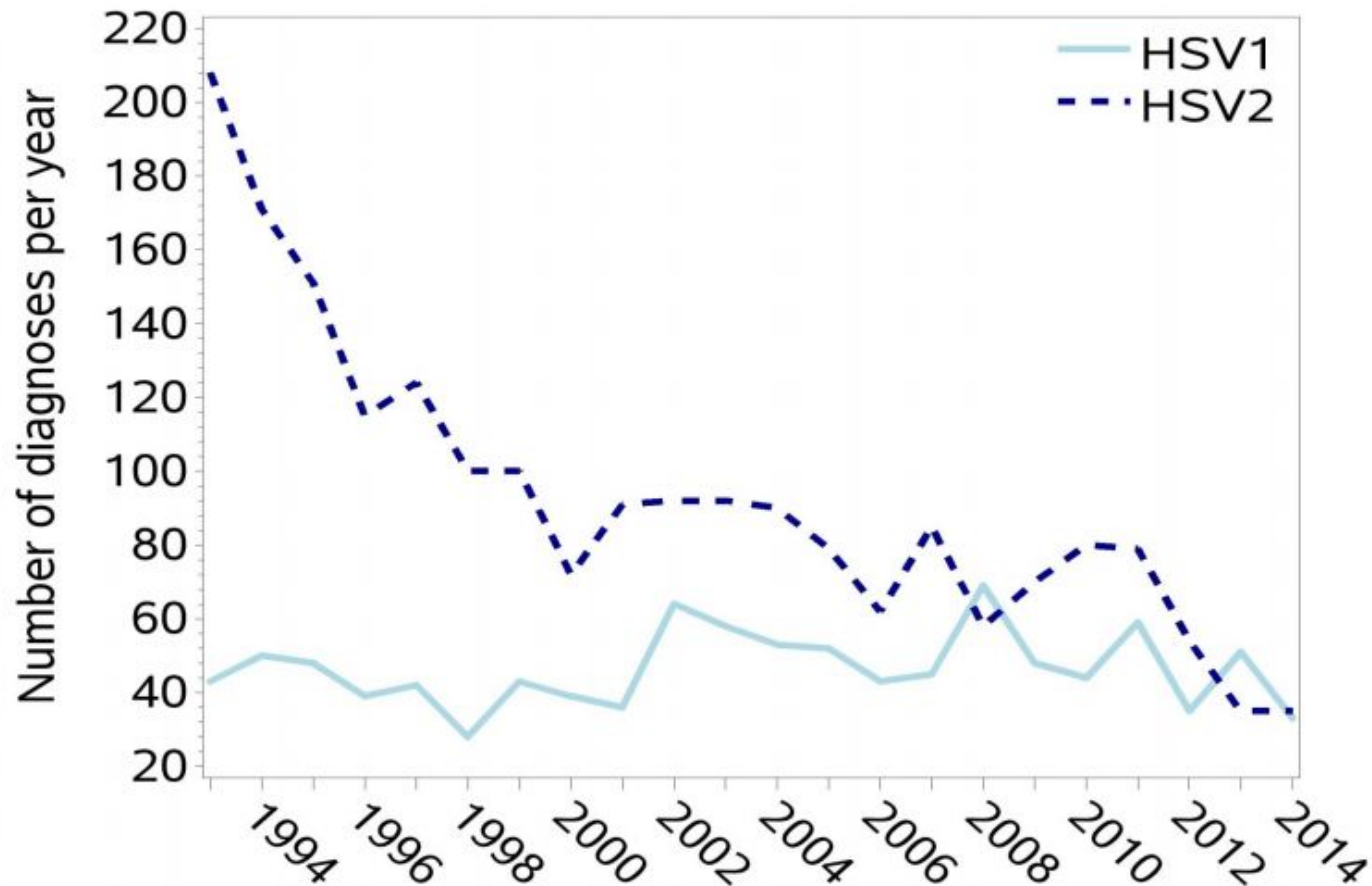
	2012	2013	2014	2015	2016
	N=149 [^]	N=143 [^]	N=359	N=306	N=339
AZM MIC ₅₀	0.25 µg/mL	0.25 µg/mL	0.25 µg/mL	0.25 µg/mL	0.25 µg/mL
AZM MIC ₉₀	0.5 µg/mL	0.5 µg/mL	1.0 µg/mL	1.0 µg/mL	1.0 µg/mL
Geometric Mean	0.21 µg/mL	0.23 µg/mL	0.30 µg/mL	0.29 µg/mL	0.27 µg/mL
MIC ≥2 µg/mL	0	0	19 (5.3%)	12 (3.9%)	15 (4.4%)
MIC ≥1 µg/mL	5 (3.4%)	4 (2.8%)	26 (7.2%)	20 (6.5%)	20 (5.9%)

*AZM: azithromycin; MIC: minimal inhibitory concentration

[^]Only urethral isolates

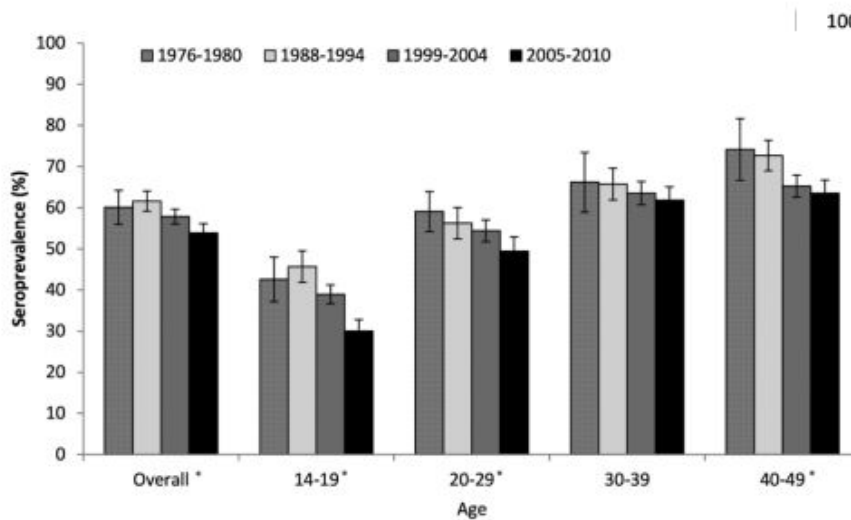
Herpes Epidemiologic Trends

Confirmed first episode genital HSV diagnoses in the Public Health – Seattle & King County STD Clinic: 1994-2014

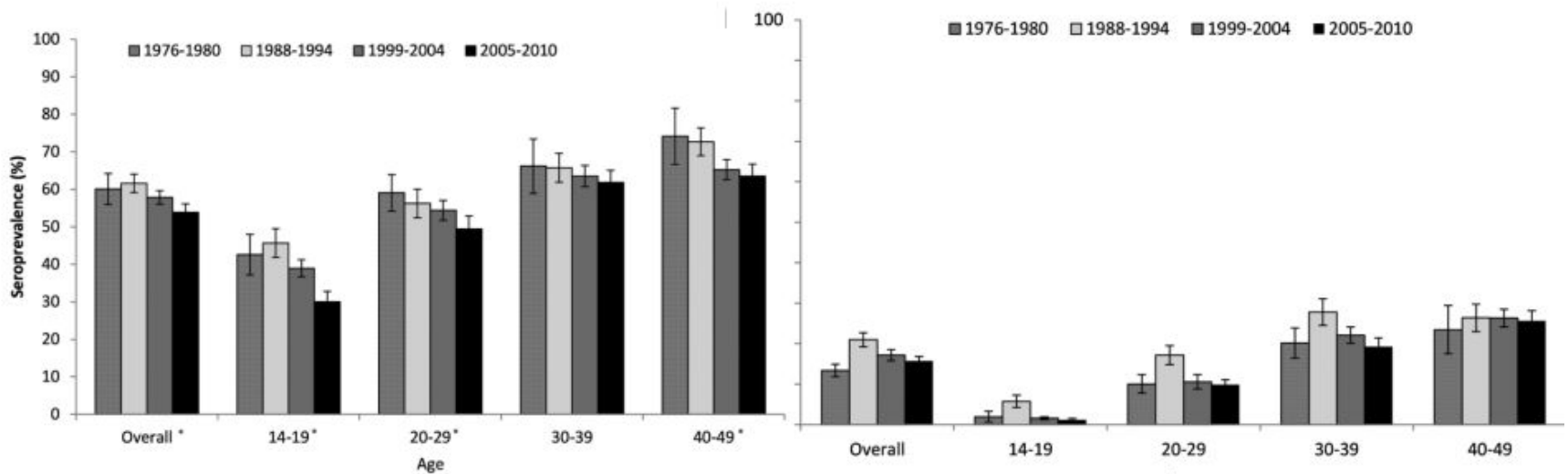


Herpes Epidemiologic Trends

HSV-1



HSV-2



5 THINGS ALL CLINICIANS SHOULD BE DOING



Level of Controversy

NONE



HIGH

#1: Extragenital Screening in MSM

- All sexually active MSM and transgender or non-binary persons who have sex with men
- Any rectal or pharyngeal exposure in past year
- Screen at least annually, or
- Screen Q3 months if any of the following:
 - Bacterial STD in the past year
 - Methamphetamine or popper use in past year
 - ≥ 10 sex partners (oral or anal) in the past year
 - Condomless anal intercourse with an HIV serodiscordant partner in the past year
 - Taking PrEP

Self-Testing Option

Seattle
STDA/HV

TEST YOURSELF

The Visual Guide for a
Self-collected Rectal Swab






- 1 Wash your hands with soap and water.
- 2 Remove the transport tube and collection vials from packaging.
- 3 Label the transport tube with your Patient label.
- 4 Label the transport tube with the Rectal label.
- 5 Open the package containing the collection vials.
- 6 Hold the collection vial above the toilet to the side to fill.
- 7 Get into a comfortable position that allows you access to your rectum. Putting your feet on the stool may help.
- 8 Gently insert the swab 1 inch into the rectum and turn the swab in a circle at least 5 times.
- 9 Remove the cap from the transport tube.
- 10 Place the collection vial into the transport tube, wrapping it as instructed.
- 11 Put the cap back on the transport tube and twist it closed to prevent leaks.
- 12 Put the transport tube into the transport bag.
- 13 Wash your hands with soap and water.

Seattle
STDA/HV

TEST YOURSELF

The Visual Guide for a
Self-collected Throat Swab



- 1 Wash your hands with soap and water.
- 2 Remove the transport tube and collection vials from packaging.
- 3 Label the transport tube with your Patient label.
- 4 Label the transport tube with the Throat label.
- 5 Open the package containing the collection vials.
- 6 Hold the collection vial far enough from the tip.
- 7 Say "Ahhh" and reach the collection swab into your throat to gently touch your throat.
- 8 Gently rub the swab tip on your throat side to side, up and down at least 5 times.
- 9 Remove the cap from the transport tube.
- 10 Place the collection vial into the transport tube, wrapping it as instructed.
- 11 Put the cap back on the transport tube and twist it closed to prevent leaks.
- 12 Put the transport tube into the transport bag.
- 13 Wash your hands with soap and water.

Email aradford@uw.edu for free posters for your clinic

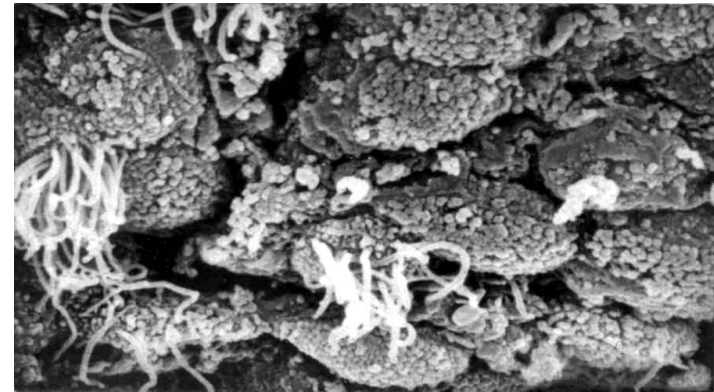
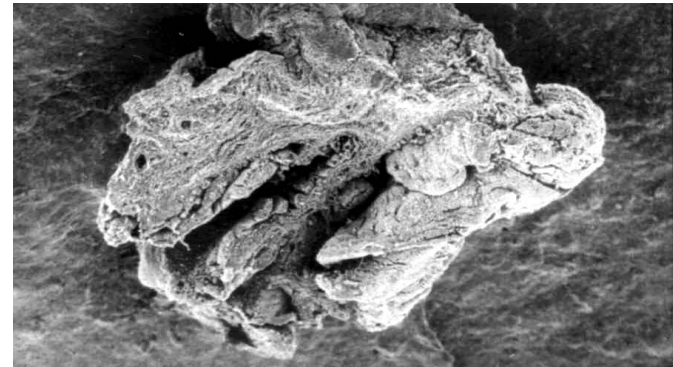
#2: Screen Women for *Chlamydia*

- All women <25 years of age
- All pregnant women
- Retest at 3 months due to risk of reinfection
- Goal = prevent infertility, ectopic pregnancy, chronic pelvic pain
- Most (>90%) women infected with chlamydia have no signs or symptoms
- NAAT sensitivity: vaginal > urine > cervix

Normal Fallopian tubes by Scanning EM



Fallopian tubes by EM after *C. trachomatis* infection



Partner Notification & Treatment

- Sex partners from past 60 days should be evaluated, tested, and treated
- Expedited partner therapy (EPT) for GC/CT
 - Increases likelihood that partners are treated and decreases reinfection rates
 - Probably decreases community-level gonorrhea and chlamydia rates
 - Legal in Washington State since 2004

#3: Treat STD Contacts Empirically

- Rationale
 - High pre-test probability
 - High transmissibility: ~30% per sex act for syphilis
 - Syphilis screening can be negative in early infection
 - RPR+ in ~85% of primary syphilis cases, so $\geq 15\%$ of infected persons will be negative prior to chancre development
 - Public health imperative to prevent ongoing transmission
- Please do not just test and send out!

#4 Confirm Positive Herpes Serologies

- Commercially available ELISA test for HSV:
Index value >1.1 = positive
- But index values 1.1-3.0 often due to cross reactivity with HSV-1
- Any positive ELISA for HSV-2: **51% positive predictive value**
- Do not give a patient a diagnosis of genital herpes based on a positive ELISA test alone

#4 Confirm Positive Herpes Serologies

- Better approach: interpret based on index value >2.0
- Best approach: confirm with Western Blot



UNIVERSITY OF WASHINGTON
VIROLOGY RESEARCH CLINIC

Where can I get tested?

If you are having oral or genital lesions, these can be tested for HSV by PCR/NAAT or culture through your local healthcare provider. Tests for HSV antibodies may also be available through your local healthcare provider. You can have your blood tested with a Western Blot at the [University of Washington Virology Lab](#). To do this, you or your health care provider can call 206-520-4600 to request the HSV Type-Specific Serology information packet.

For more information, see the Herpes Blood Tests Quick Reference Guide provided by the American Social Health Association.

[\(top\)](#)

- New tests in development for broader use

#5 Screen for and Rapidly Evaluate & Treat Complicated Syphilis

- Complicated Syphilis
 - Neurosyphilis (asymptomatic or symptomatic)
 - Ootosyphilis
 - Ocular Syphilis
- Key Questions:
 - Change in vision or photophobia?
 - Change in hearing?
 - New or changed tinnitus?
 - Difficulty walking?

Association between mild or greater severity symptoms and neurosyphilis (+CSF VDRL) among 81 HIV+ and 385 HIV- patients referred to UW neurosyphilis study (PI: Marra)

Symptom	Odds Ratios (95% Confidence Interval)	
	HIV-Uninfected	HIV-Infected
Headache ^a	0.6 (0.2–1.8)	0.8 (0.5–1.5)
Stiff neck ^a	1.0 (0.2–4.2)	0.8 (0.4–1.7)
Photophobia ^a	0.5 (0.1–2.5)	2.0 (1.1–3.8)*
Vision loss ^a	1.6 (0.6–4.6)	2.3 (1.3–4.1)**
Ocular inflammation ^a	0.5 (0.1–1.9)	1.1 (0.6–2.0)
Hearing loss ^a	0.8 (0.2–2.4)	1.5 (0.8–2.8)
Sensory loss ^a	1.2 (0.2–6.9)	1.9 (0.6–6.2)
Gait incoordination ^a	1.3 (0.4–3.9)	2.4 (1.3–4.4)**

Abbreviation: HIV, human immunodeficiency virus.

* $P = .03$, ** $P = .003$, *** $P = .006$.

^aMild or greater severity.

>=Moderate severity hearing loss: OR 3.1 (1.3 - 7.5)

#5 Screen for and Rapidly Evaluate & Treat Complicated Syphilis

Key Steps:

- Lumbar puncture
 - Can be normal in ocular and oto-syphilis
- If vision symptoms: urgent ophthalmologic eval
- If hearing symptoms: urgent audiologic eval
- Treatment
 - Do not delay treatment for evaluation
 - Give Bicillin if plan is uncertain at end of visit
- Normal LP + normal ophtho exam rules out ocular syphilis
- Ootosyphilis is a clinical diagnosis – cannot be ruled out

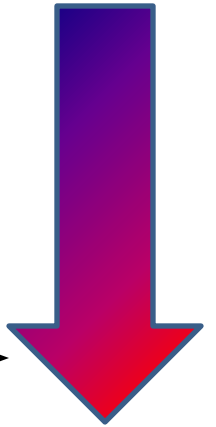
Review of 5 Things All HIV Clinicians Should be Doing

- Extragenital screening in MSM
- Screening women <25 (or pregnant) for Chlamydia
- Treating STD contacts empirically
- Confirming herpes serologic tests
- Screening for and rapidly evaluating & treating complicated syphilis

4 CLINICAL CONTROVERSIES



Level of
Controversy



Controversy #1: Extragenital screening in women

- Women get extragenital GC & CT
- *Isolated* extragenital infections less common than in MSM
- Frequent enough to raise question of screening

Summary of 14 studies of women attending sexual health clinics

Rectal CT+ overall 6.0% (95% CI: 3.2 – 8.9%)

Rectal CT+, among urogenital CT+ 68.1% (95% CI: 56.6 – 79.6%)

Rectal CT+ and urogenital CT- 2.2% (95% CI: 0 – 5.2%)

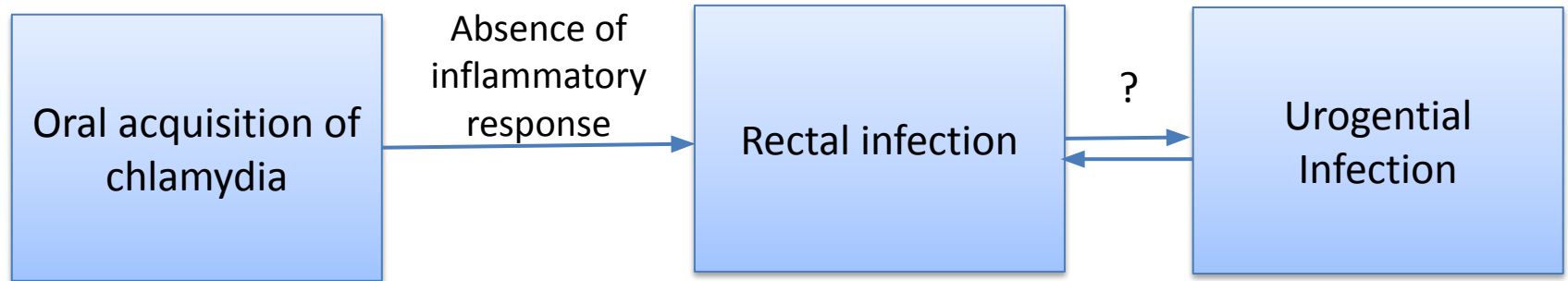
Controversy #1: Extragenital screening in women

- Rectal chlamydia is **not associated with anal sex in women**
- Summary risk ratio: 0.90 (95% CI: 0.75 – 1.10)
- Hypothesis based on *C. muridarum* (*mouse chlamydia*)



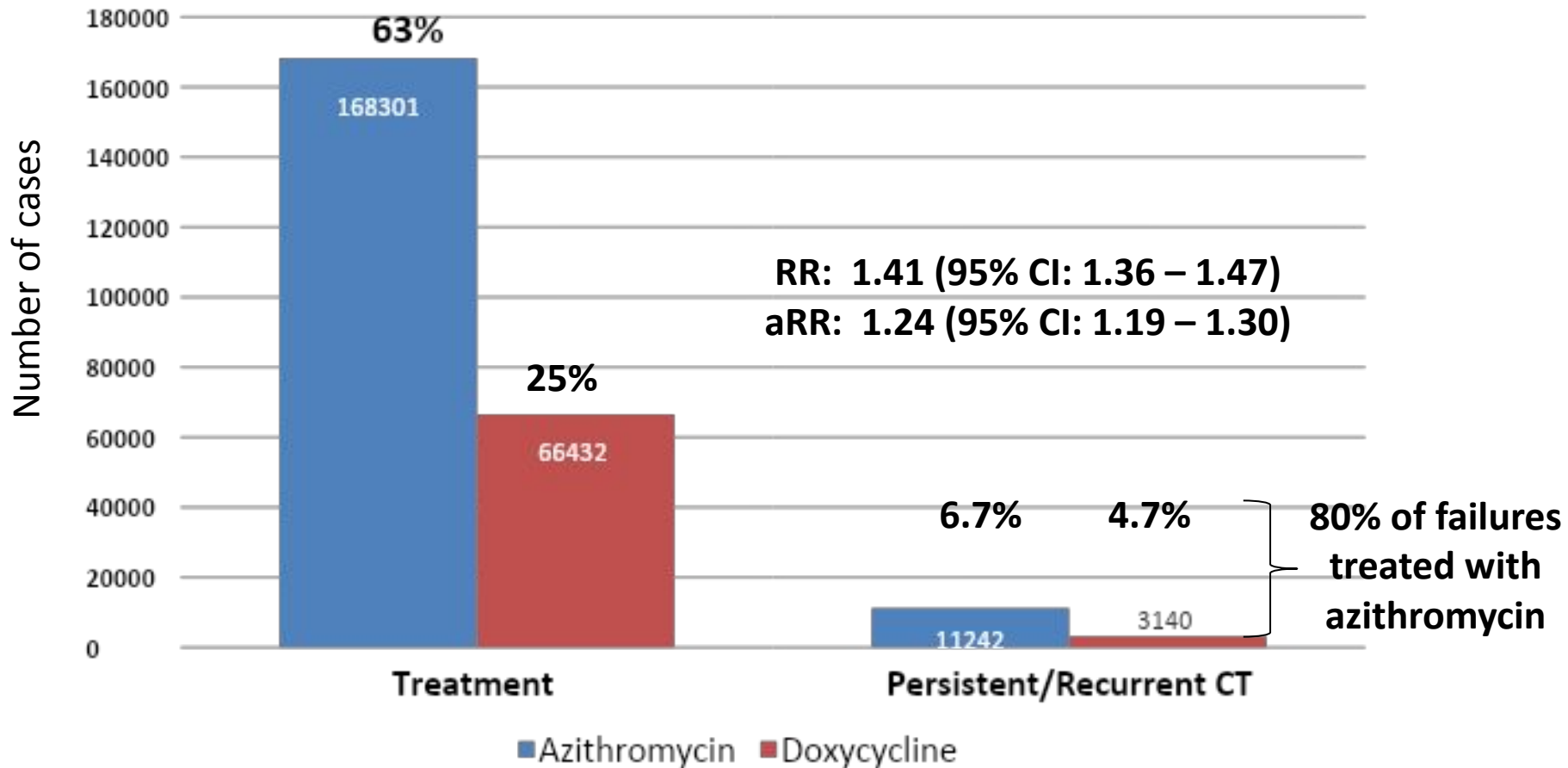
Controversy #1: Extragenital screening in women

- Unclear clinical & public health significance of rectal CT



- If rectal infection is contributing to urogenital CT infection, and
- If azm is inferior to doxy for treatment of rectal CT, then
- Would expect differential failure with azm vs. doxy for treatment of urogenital CT

Risk of persistent/recurrent urogenital CT 14-180 days after treatment, by treatment received among women in WA State, 1992-2015 (N=268,596)



Controversy #1

Should we screen women for extragenital GC and CT?

My opinion: not yet

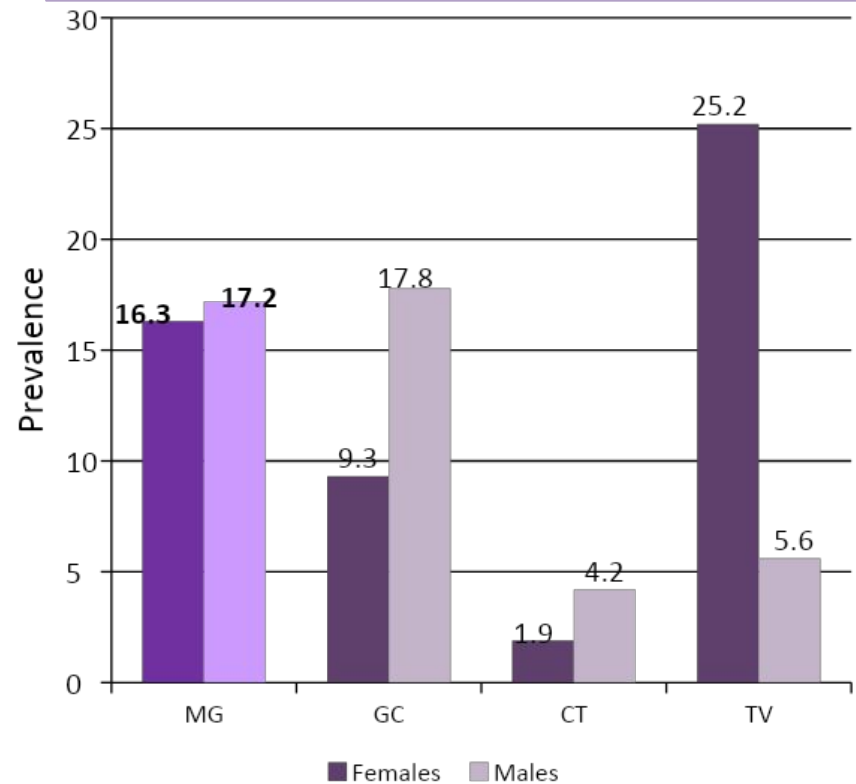
Controversy #2: Testing for *Mycoplasma genitalium*

Population prevalence (age 18-27), U.S.

<i>M. genitalium</i>	1.0% (1.1% M, 0.8% F)
<i>C. trachomatis</i>	4.2%
<i>N. gonorrhoeae</i>	0.4%
<i>T. vaginalis</i>	2.3%

Manhart et al, AJPB 2007

Prevalence in Clinical Populations (Clinical Diagnostic Test Assessment Study)



Getman et al, J Clin Micro 2016

M. genitalium Associations with STI Syndromes

Syndrome	Summary risk estimate OR (95% CI)	Studies accounting for CT (subset)
NGU	5.5 (4.3 – 7.0)	-
Female Urethritis	2.2 (1.6 – 2.9)	2.1 (1.5 – 2.9)
Cervicitis	1.6 (1.4 – 2.0)	1.9 (1.4 – 2.8)
PID / Endometritis	1.9 (1.3 – 3.5)	2.0 (0.95 – 4.0)
Preterm Delivery	1.9 (1.2 – 2.9)	2.3 (1.1 – 5.0)
Spontaneous Abortion	1.8 (1.1 – 3.0)	2.3 (1.0 – 4.9)
Infertility	3.0 (1.3 – 6.7)	3.7 (1.7 – 8.1)
HIV	2.0 (1.4 – 2.8)	-

M. genitalium Treatment

Antibiotic	Approximate cure rates	Notes
Doxycycline 100mg BID x 7d	30-40%	Despite in vitro susceptibility
Azithromycin 1g po x 1	40%	Rapidly emerging resistance: ~40-50% in US settings
Moxifloxacin	100% (initially), 69-88% (more recently)	Rapidly emerging resistance: 20% in 2011 to 47% in 2013 in Japan
Pristinamycin 1g QID x 10 days	?	Not available in US Now treatment failures in Australia
Spectinomycin 2g IM x 7 days	?	Successful in 1 case report

Nongonococcal Urethritis Treatment

European & Australian guidelines recommend *M. gen* testing, preferably with macrolide resistance testing. U.S. guidelines do not.

Australian Guidelines

Doxycycline +
M gen testing w/ macrolide
resistance testing



Followed by:
Moxifloxacin 400mg x 7 days
Or
Azithromycin 1g x1 then
500mg daily x 3 days

Persistent or recurrent NGU (*M. gen*
most common cause)

Persistent or
recurrent
NGU

King County STD Clinic

Doxycycline
or azithromycin



Moxifloxacin 400mg x 7 days

Guidelines assume
microscopic assessment to
differentiate NGU from
gonococcal urethritis

Controversy #3: Single Dose Azithromycin

- Growing resistance among GC
- Less effective for rectal CT and symptomatic urogenital CT
- High and increasing resistance in *M. genitalium*

Maybe we need to stop using single dose azithromycin in STD treatment!

Counterpoint: cheap, easy, high adherence

WHAT'S COMING NEXT?

What Tools do we Have for STI Prevention?



Counseling & Education

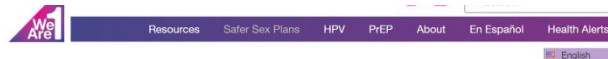


Condom promotion



Frequent testing & treatment

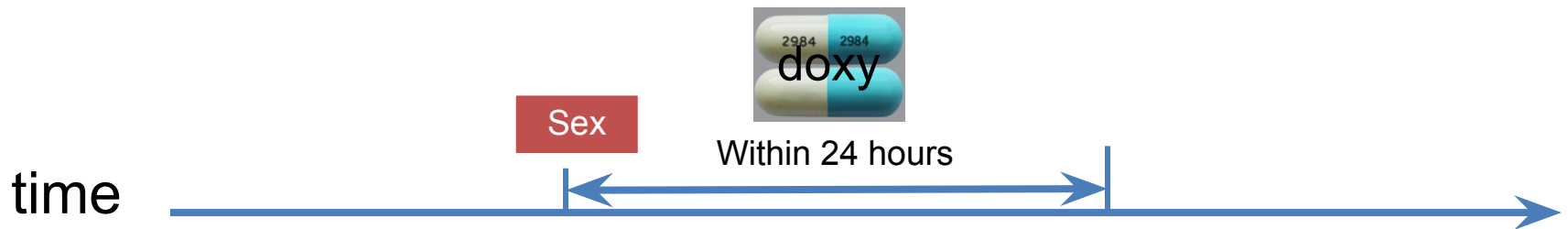
Combination prevention



Doxycycline for STI Prevention

- Studied as both post- & pre-exposure prophylaxis

Post-exposure prophylaxis

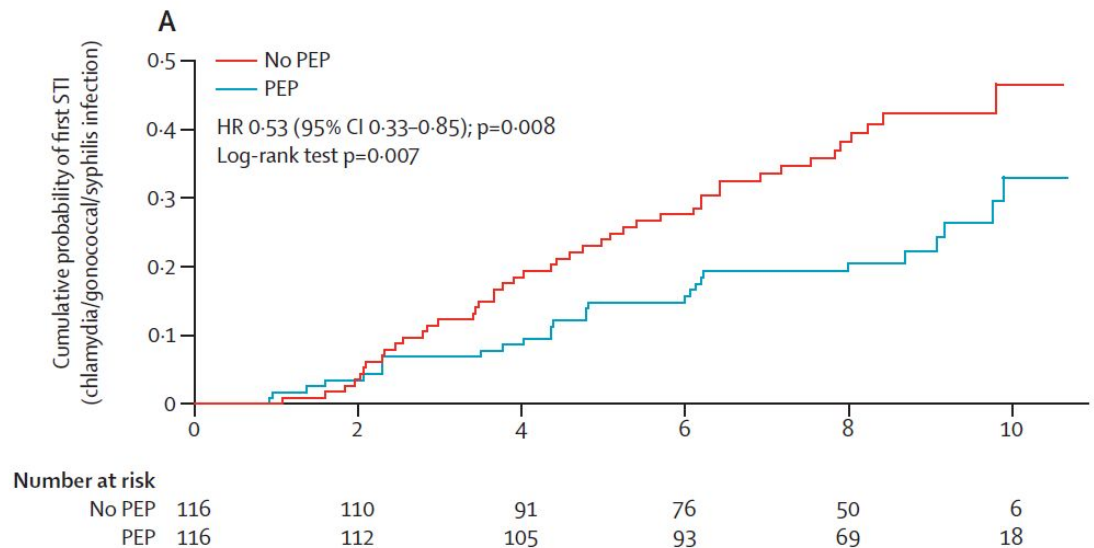


- No resistance to doxycycline among *C. trachomatis* or *T. pallidum*
- Resistance among *N. gonorrhoeae* varies

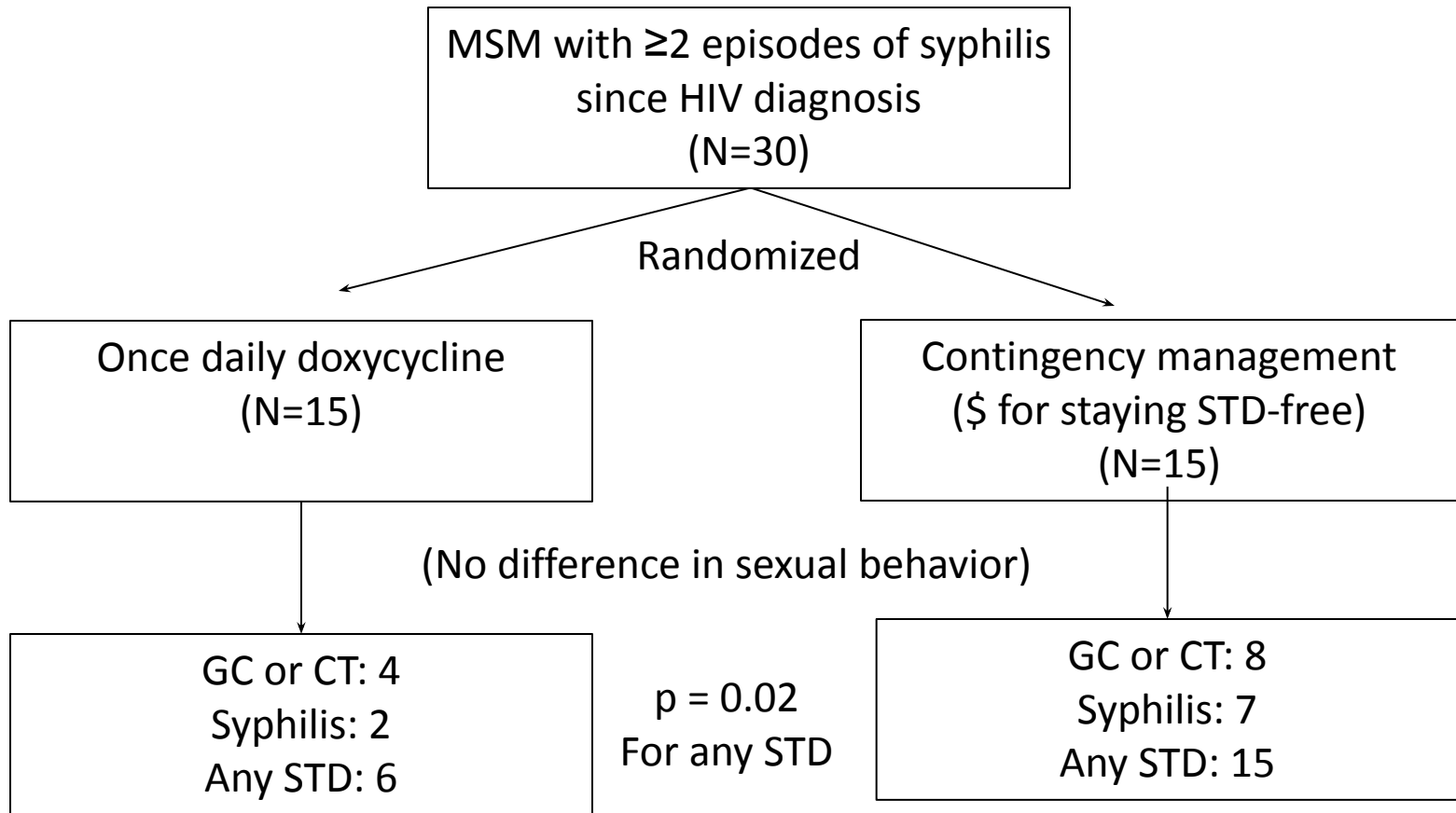
Doxycycline Post-Exposure Prophylaxis

- RCT in open label extension of IPERGAY PrEP study
- Doxy 200mg x1 ~24h after sex (≤ 72 h)
- Targeting CT & syphilis
- \downarrow time to first STI
- No risk compensation
- 7% discontinuation
- Median 7 pills/month (IQR: 3-15)

Kaplan-Meier estimates of time to first STI by study group



Doxycycline Pre-Exposure Prophylaxis



Doxycycline for STI Prevention

- Very preliminary data
- Big potential downsides
 - Antimicrobial resistance (STIs or microbiome)
 - Adverse effects
- Most STIs in MSM do not cause substantial morbidity (easily cured w/o long-term effect)

Patient Interest in Doxy PEP

Willingness to use doxycycline PEP

- Grindr survey in 6 US cities
 - 89% of HIV+
 - 86% HIV-
- San Francisco
 - 75% of HIV+ (Ward 86)
 - 90% of HIV- [City Clinic (STD Clinic)]
- Seattle
 - 90% of STD Clinic PrEP patients

GC Drug Pipeline

- Solithromycin
 - Fluroketolide, Phase III trial underway
- Zoliflodacin
 - Topoisomerase inhibitor, Phase II trial complete
- Gepotidacin
 - Topoisomerase inhibitor, Phase II trial complete

Summary

- Epidemiology
 - Major increases in STI rates, mostly among MSM but also among women & heterosexual men
 - In the context of decreasing HIV
- Clinicians' role is crucial!
 - Extragenital screening, CT screening in women, partner treatment, detection of complicated syphilis
- Need new tools
 - Herpes diagnosis, ?doxy PEP, new GC drugs

RESOURCES

STD/HIV Prevention Training Center Online Consult Request



National Network of
STD Clinical Prevention
Training Centers

STD Clinical Consultation Network

Important for Requestors to Consider

The Clinical Consultation Service is intended for licensed healthcare professionals and STD program staff. We do not provide direct medical care, treatment planning, or medical treatment services to individuals.

The information provided through the Clinical Consultation Service is not a replacement for local expertise or your state STD program protocols. Information is offered as clinical decision support, is advisory in nature and is not intended to replace local healthcare decision-making or provision. Requestors are free to disregard any advice offered. Final clinical decisions are the sole responsibility of the healthcare provider.

Please note, consults placed after 4 pm may not be triaged until the next business day and responses may be delayed during holiday periods.

stdccn.org

National STD Curriculum

www.std.uw.edu

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