Thomas Jefferson University
Jefferson Digital Commons

Department of Family & Community Medicine Presentations and Grand Rounds | Department of Family & Community Medicine

4-29-2020

STI & PrEP Updates

Marshal Miller, MD, AAHIVS

Sunny Lai, MD

Follow this and additional works at: https://jdc.jefferson.edu/fmlectures

 Part of the Family Medicine Commons, and the Primary Care Commons

Let us know how access to this document benefits you

This Article is brought to you for free and open access by the Jefferson Digital Commons. The Jefferson Digital Commons is a service of Thomas Jefferson University's Center for Teaching and Learning (CTL). The Commons is a showcase for Jefferson books and journals, peer-reviewed scholarly publications, unique historical collections from the University archives, and teaching tools. The Jefferson Digital Commons allows researchers and interested readers anywhere in the world to learn about and keep up to date with Jefferson scholarship. This article has been accepted for inclusion in Department of Family & Community Medicine Presentations and Grand Rounds by an authorized administrator of the Jefferson Digital Commons. For more information, please contact: JeffersonDigitalCommons@jefferson.edu.

STI & PrEP Updates

Marshal Miller, MD, AAHIVS

Sunny Lai, MD, MPH

April 29, 2020

Lecture Objectives

- Apply key findings from the DISCOVER trial to PrEP clinical decision-making
- Understand the gaps in PrEP research for cisgender women and adolescents
- Understand the use of on-demand pre-exposure prophylaxis
- Review Current treatment recs and emerging data on Gonococcal and Chlamydial infection
- Discuss diagnostic and management options for non-gonococcal urethritis

Case 1: Switching to Descovy for PrEP?

- 20-year-old man presents for his three-month PrEP visit.
- He has been seeing a lot of lawsuit ads on TV that Truvada is dangerous.
- He heard that Descovy is now an option.
- He asks for your opinion about switching to Descovy.
- How would you advise him?

PrEP Timeline

- **2012:** FDA approved Truvada for HIV pre-exposure prophylaxis for adults at risk for acquiring HIV
- **2018:** Truvada was approved for adolescents weighing at least 35 kg
- **2019:** USPSTF made a level A recommendation to offer PrEP to persons at high risk of HIV acquisition
- **2019:** FDA approved Gilead's Descovy for PrEP for MSM and TGW, not for cis women who engage in receptive vaginal sex

https://www.statnews.com/2020/02/26/newest-prep-pill-hiv-prevention-fuel-progress-or-profits/

CDC, 2018; FDA Briefing Document, 2019; USPSTF, *JAMA, 2019.*

Truvada vs. Descovy

Name	Tenofovir	Emtricitabine	Renal Function	Population
Truvada	Tenofovir disoproxil fumarate (TDF) 300 mg	Emtricitabine (FTC), 200 mg	Not recommended if CrCl <60 mL/min	MSM TGW Heterosexual PWID
Descovy	Tenofovir alafenamide (TAF) 25 mg	Emtricitabine (FTC), 200 mg	Not recommended if CrCl <30 mL/min	MSM TGW

Prescribing PrEP

Gay, Bisexual, and other Men who have Sex with Men, and Transgender Women	Heterosexual Men and Women	People who inject drugs
• Sexual partner with HIV • Recent bacterial STD • High number of sex partners • History of inconsistent or no condom use • Commercial sex work	• Sexual partner with HIV • Recent bacterial STD • High number of sex partners • History of inconsistent or no condom use • Commercial sex work • Lives in high prevalence area or network	• HIV-positive injecting partner • Sharing injection equipment • High risk sexual behavior

Descovy and Truvada: approved for adolescents (>35 kg)
Truvada is safe in use in pregnancy and breastfeeding

PrEP Labs and Monitoring

Lab Screening and Visits			
Initial visit	• HIV test (ideally 4th gen HIV ag/ab) • Cr • HbsAb/Ag • HAV Ab • HCV Ab	• Pregnancy test • GC/CT (site-specific) • Syphilis	• Offer HAV, HBV and HPV immunization as indicated
Week 1	Call, check if Rx filled, assess adherence and side effects		
Month 1 (optional)	Assess adherence and side effects		
Every 3 months	• HIV testing, assess s/sx of acute HIV • Repeat pregnancy test for women who may become pregnant • STI testing		
At least every 6 months	CrCl		
At least every 12 months	Evaluate need to continue PrEP		

Time to steady state levels of TFV-DP:

Maximum intracellular concentrations of TFV-DP are reached in:

- Blood after 20 days of daily oral dosing
- Rectal tissue after 7 days of daily oral dosing
- Cervico-vaginal tissues at 20 days of daily oral dosing

CDC 2017

Side effects

SHORT TERM

	DRUG	PBO
diarrhea	7%	8%
abdominal pain	4%	2%
back pain	5%	5%
headache	7%	6%
depression	6%	7%
anxiety	3%	3%
weight loss	3%	2%

Early side effects were mild, usually resolved within first month.

Side effects may be due to non-adherence.

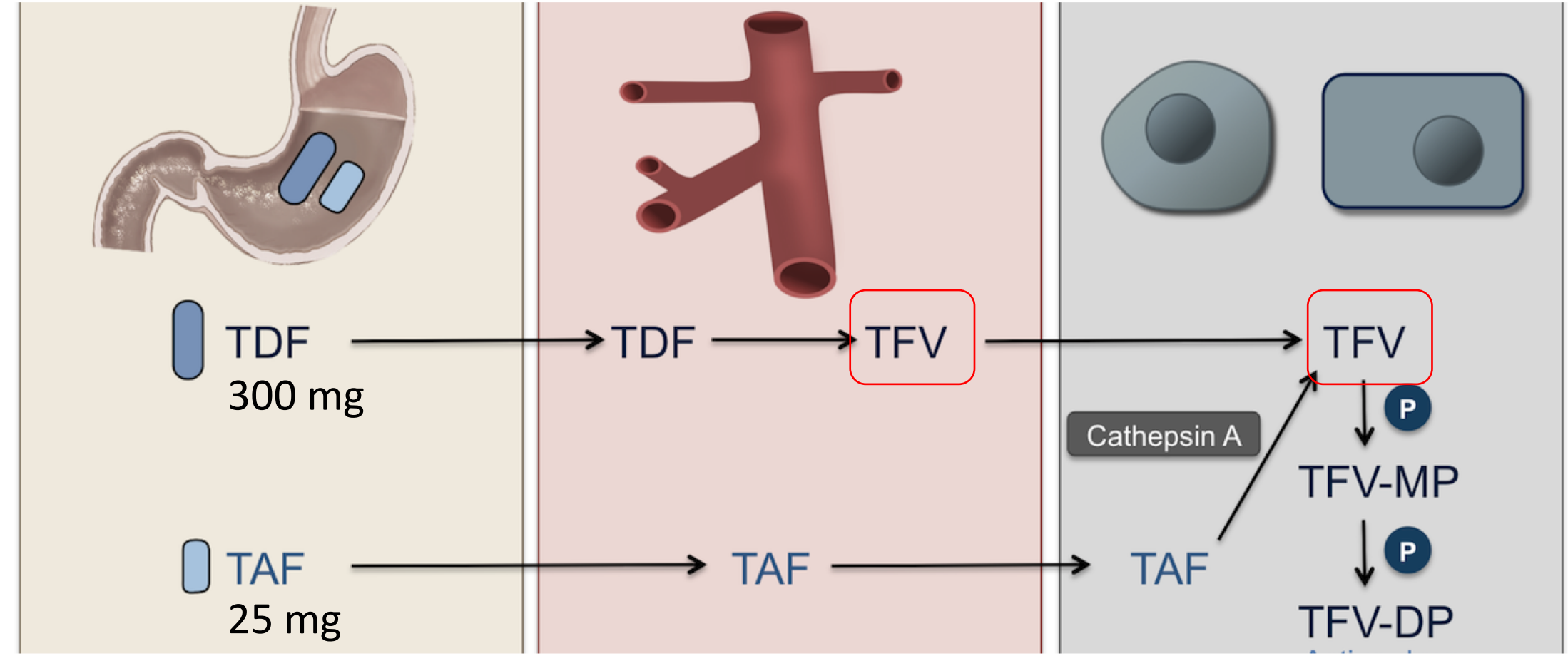
LONG TERM

- Those in iPrEx who took Truvada generally showed 1–2% bone loss within first few months. Bone loss also seen in those on placebo.
- People with existing kidney dysfunction (<60 ml/min eCrCl) should probably not start Truvada.
- People on Truvada who show abnormal kidney function test results may want to stop Truvada.
- iPrEX participants who experienced kidney dysfunction saw kidney health return to normal after stopping.
- To prevent kidney damage, kidney function tests are done every 6 months.

Image credit: Please PrEP Me Navigator Manual

Metabolism of TDF vs. TAF

Image Credit: University of Washington, National HIV Curriculum



Safety Profiles of TDF vs. TAF
(Studies in PLWH)

[1]Gupta et al. *AIDS.* 2019
[2]Grant, P and Cotter, A. *Curr Opin HIV AIDS.* 2016; [3]Wang et al. *Medicine.* 2016; [4]Sax et al. *Clin Infect Dis.* 2019

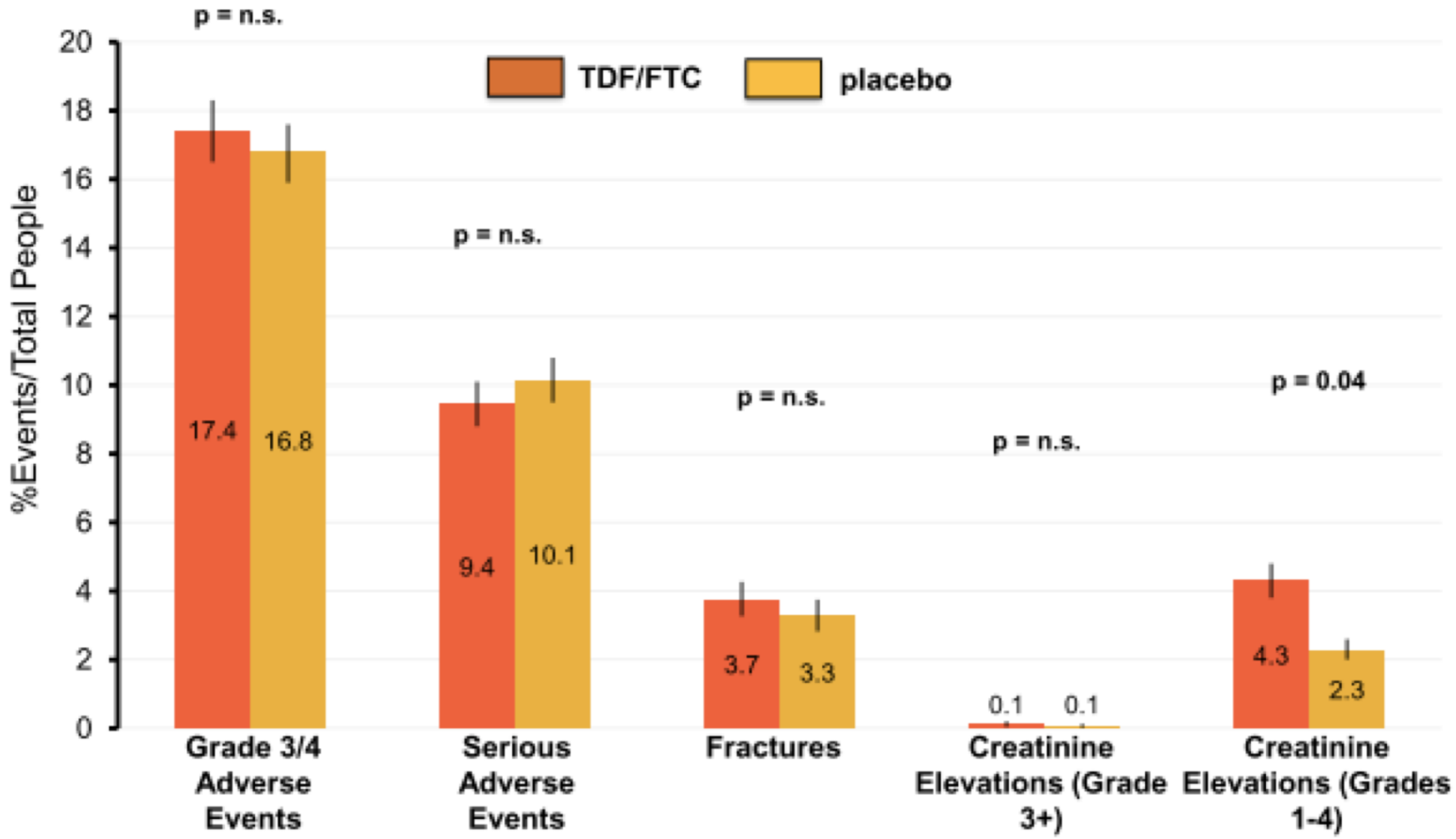
TDF

- Renal Toxicity: ⇧ Prox. Tubule Dysfunction, GFR, Cr[1-3]
- Bone Toxicity: ⇩ BMD[2,3]
- ⇔ Weight[4], ⇔/⇧ Lipids[3]

TAF

- More favorable renal and bone profile[1-3]
- ⇧ Weight[4]
- ⇧ TC, LDL, HDL; ⇔ TC:HDL[3]

What's the safety data in people on PrEP?



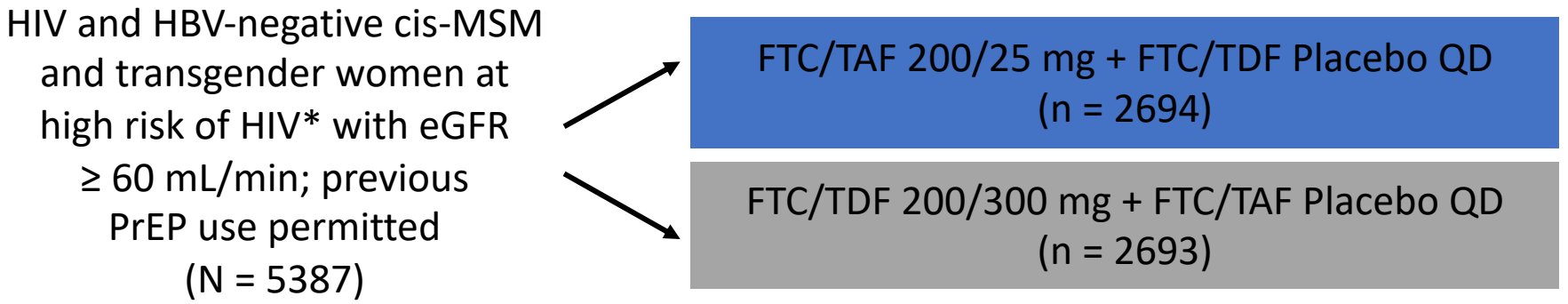
Grade 1 Cr: 1.1-1.3x upper limit of normal

Grade 2 Cr: 1.1-1.8x upper limit of normal

Pilkington et al. *J Virus Erad.* 2018

DISCOVER: Study Design

- International, randomized, double-blind, active-controlled non-inferiority phase III trial



- Prevention services (eg, risk reduction, condoms/lubricant) and adherence counseling provided at entry and every 12 wks
- Endpoints of current analysis: HIV incidence and safety, including renal AEs and biomarkers, bone fractures, BMD, and metabolic parameters at Wk 96

Ogbuagu. CROI 2020. Abstr 92.

Slide credit: clinicaloptions.com

DISCOVER: Baseline Characteristics

Characteristic	FTC/TAF (n = 2694)	FTC/TDF (n = 2693)
Median age, yrs (range)	34 (18-76)	34 (18-72)
Race, n (%)		
▪ White	2264 (84)	2247 (84)
▪ Black	240 (9)	234 (9)
▪ Asian	113 (4)	120 (5)
Hispanic/Latinx ethnicity, n (%)	635 (24)	683 (25)
Transgender woman, n (%)	45 (2)	29 (1)
HIV risk factors, n (%)		
▪ Condomless receptive anal sex with ≥ 2 partners in past 12 wks	1616 (62)	1569 (60)
▪ Rectal gonorrhea in past 24 wks	274 (10)	262 (10)
▪ Rectal chlamydia in past 24 wks	342 (13)	333 (12)
▪ Syphilis in past 24 wks	230 (9)	263 (10)
▪ Recreational drug use in past 12 wks	1785 (67)	1786 (67)
▪ Binge drinking (≥ 6 drinks on ≥ 1 occasion; ≥ 1 time/mo)	618 (23)	599 (22)
Taking FTC/TDF for PrEP at baseline, n (%)	465 (17)	440 (16)

Ogbuagu. CROI 2020. Abstr 92.

Slide credit: clinicaloptions.com

FTC/TAF is non-inferior to FTC/TDF

- Noninferiority of FTC/TAF vs FTC/TDF for HIV prevention at Wk 96 established
  - Upper bound of 95% CI of incidence rate ratio < 1.62

HIV Incidence	FTC/TAF (n = 2670)	FTC/TDF (n = 2655)
Current analysis at Wk 96†		
HIV infections, n	8	15
PY of follow-up	5029	5052
HIV incidence/100 PY	0.16	0.30
Incidence rate ratio for FTC/TAF vs FTC/TDF (95% CI)	0.54 (0.23-1.26)	

Ogbuagu. CROI 2020. Abstr 92.

Slide credit: clinicaloptions.com

DISCOVER: Safety Data Through Wk 96

- Both regimens well tolerated with low rates of discontinuation for AEs (1% to 2%)
- FTC/TAF associated with statistically significantly more favorable renal and bone safety outcomes vs FTC/TDF
  - More favorable $eGFR_{CG}$ changes in overall population, participants aged ≥ 50 yrs, and participants with BL CrCl 60 to ≤ 90 mL/min ($P < .001$ for PrEP regimen comparison in each group)
    - FTC/TAF: -0.6 mL/min vs. FTC/TDF: -4.1 mL/min
  - More favorable spine and hip BMD changes through Wk 96 ($P < .001$)
    - FTC/TAF: Spine (+1.0%), Hip (+0.6%) vs. FTC/TDF: Spine (-1.4%), Hip (-1.0%)

Ogbuagu. CROI 2020. Abstr 92.

Slide credit: clinicaloptions.com

DISCOVER: Metabolic Parameters at Wk 96

Median Change From BL at Wk 96	FTC/TAF	FTC/TDF	*P* Value
Total cholesterol, mg/dL	-3	-14	< .001
LDL cholesterol, mg/dL	-2	-7	< .001
HDL cholesterol, mg/dL	-1	-4	< .001
Triglycerides, mg/dL	+3	-4	< .001
Fasting glucose, mg/dL	+2	+2	.63
Total cholesterol:HDL ratio	+0.1	0	.18
Median body weight, kg	+1.7	+0.5	< .001

- Wk 96 median BMI: 25.9 with FTC/TAF vs 25.4 with FTC/TDF ($P < .001$)
  - BL BMI 25.3 in both arms

Ogbuagu. CROI 2020. Abstr 92.

Slide credit: clinicaloptions.com

Messaging:

- Descovy is an alternative, non-inferior, safe and effective daily oral PrEP option for men who have sex with men and transgender women who have sex with men.
- It is not superior nor a “better PrEP.”
- Can be considered in people who are at risk for renal impairment and osteoporosis, older age.

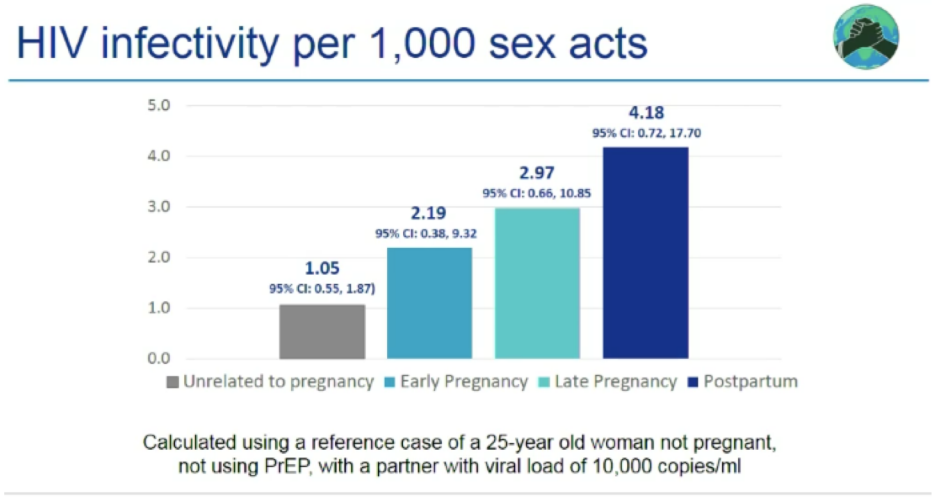
Talking Points

The importance of including cisgender women in research

- Unknown relative importance of serum vs. tissue drug levels to provide protection against HIV
- Increased risk of HIV acquisition per sex act in late pregnancy and postpartum
- There is no established safety database for TAF/FTC in pregnancy
- Concerns for increased weight gain in women on TAF.

F.D.A. Approves New H.I.V.-Prevention Drug, but Not for Everyone

Citing a lack of evidence, the agency will require Gilead to conduct additional trials in individuals 'who have receptive vaginal sex.'



CDC, 2018; UNAIDS. Fact Sheet—Global AIDS Update 2019 Published July 2019.; Thomsen et al. CROI 2018.

The importance of prescribing PrEP to cisgender women

- Globally, more than 48% of new HIV infections are among cis women.
- Cis-gender women make up 1 in 5 new HIV infections in the United States, yet fewer than 1 in 10 are on PrEP.
- Women-controlled option

Adolescents and PrEP

- 2018, FDA approved TDF/FTC (Truvada) use for adolescents weighing >35 kg (77 lbs) for pre-exposure prophylaxis

- Unique aspects of providing PrEP among adolescents:

Safety	Adherence
Legal	Cost

Provider Reference Guide for Offering STI and HIV Services, including PrEP, to Minors without Parental/Guardian Consent

Based on Explicit Language in Statute and/or Regulation

	ΔAge of Majority	Family Planning Services (N=21)	STI Diagnosis & Treatment (N=51)	STI Prevention (N=19)	HIV Testing (N=39)	HIV Treatment (N=33)	HIV Prevention (N=16)	ΔΔDisclosure Permitted (N=23)
Pennsylvania	21	✔ (18 or older)	✔	✔ (18 or older)	✔	✔	✔ (18 or older)	

✔ Provider may provide service to minor without parental or guardian consent

Hosek et al. *JAMA Ped.* 2017; Hosek et al. *J Acquir Immune Defic Syndrome.* 2017
https://www.cdc.gov/hiv/policies/law/states/minors.html

Paying for PrEP

READY, SET, PrEP

HHS launched this program in December 2019 as part of the government's "End the HIV Epidemic" initiative

Gilead's Advancing Access® Program Is Here to Help You

ADVANCING ACCESS®

	Good Days	Patient Advocate Foundation	PAN Foundation
Website	mygooddays.org	copays.org	panapply.org
Phone	214-570-3621 (fax)	800-532-5274	866-316-7263
Apply by	mail, fax	phone, online	phone, online
Income limit (single household)	500% FPL	400% FPL + cost of living adjustment	500% FPL
Residency	U.S. resident, valid SSN	U.S. resident, valid SSN	U.S. resident
Health plans covered	Medicare, VA, Tricare	insured individuals, incl. Medicare	Medicare only
Assistance limit	$7,500	$7,500	$3,400
Co-pay assistance	prescription only	prescription only	prescription only
Re-apply	every 12 months	every 12 months	every 12 months
Notes	---	start using funds within 30 days of award or they will be forfeited	often closed to new enrollment due to funding shortfalls; assists after other sources are used

Case 2: On-Demand PrEP

- 36-year-old man presents for STI screening
- MSM
- He only has sex once a month, usually planned
- Is interested in pre-exposure prophylaxis, but does not want to take a daily medication
- What do you recommend?

What do you recommend?

a) No PrEP
b) Daily TDF/FTC
c) On-demand TDF/FTC
d) Daily TAF/FTC
e) On-demand TAF/FTC

On-Demand PrEP (TDF/FTC; Truvada)

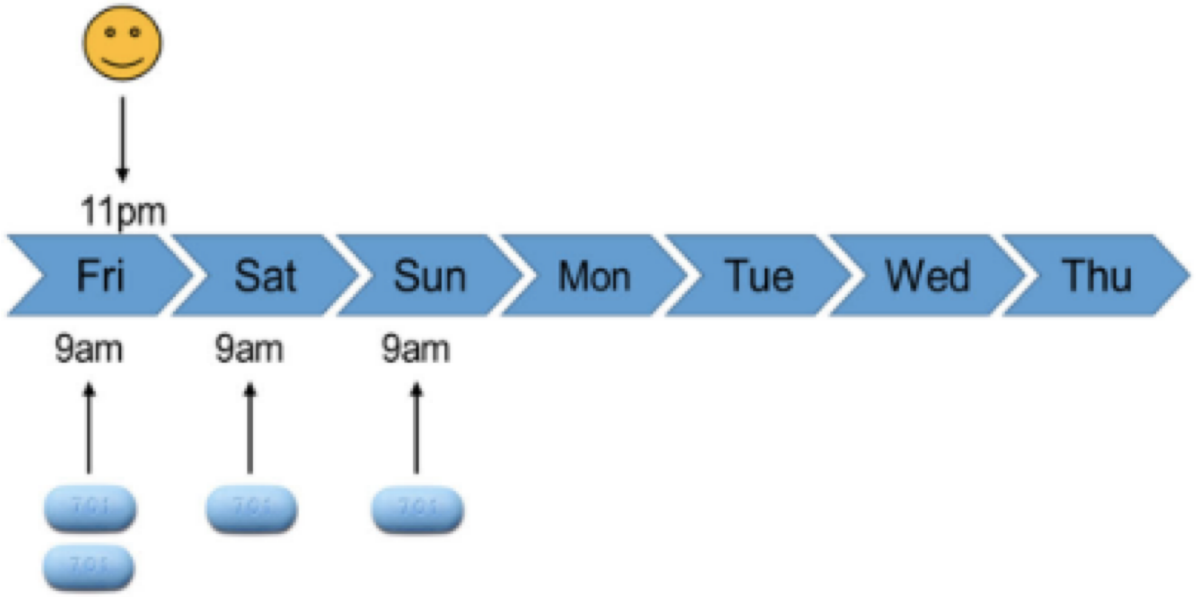
- Other terms: “non-daily PrEP,” ”event-driven PrEP,” or “2-1-1 PrEP”

- Off-label use
  - Recommended as an alternative to daily PrEP by International Antiviral Society-USA and European AIDS Clinical Society for men who have sex with men
  - Not yet recommended in the 2017/2018 CDC PrEP Guidelines

Saag et al. *JAMA.* 2018; https://eacs.sanfordguide.com/art/pre-exposure-prophylaxis; CDC, 2018

How is 2-1-1 done?

Example 1: One sex episode.
2 PrEP tablets 2-24 hours before sex; 1 PrEP tablet 24 hours after and another 48 hours after the double dose.

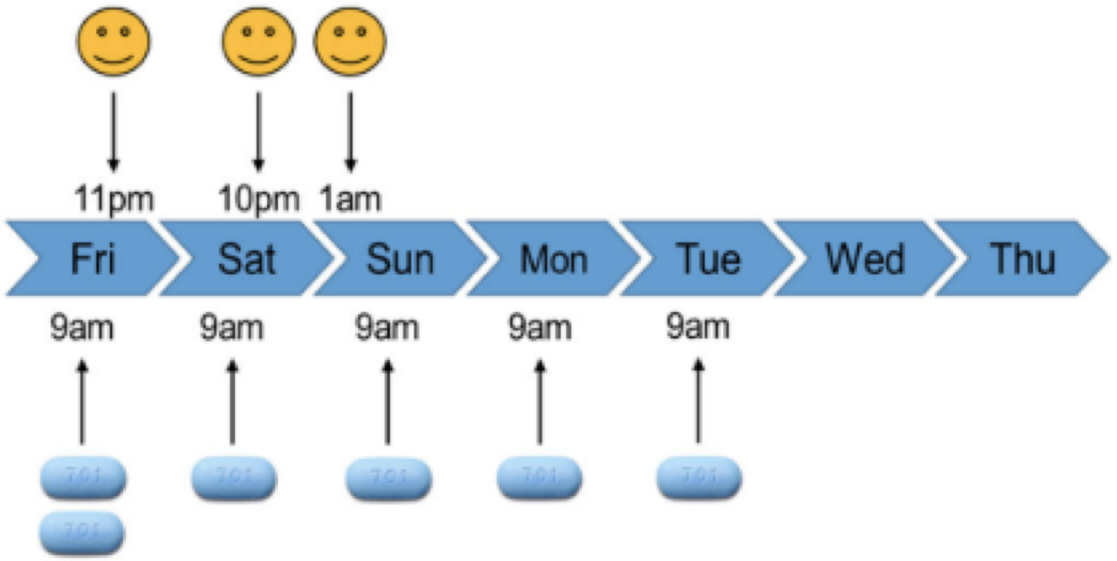


2-1-1

Saberi P. and Scott HM. *J Gen Intern Med.* 2019

How is 2-1-1 done?

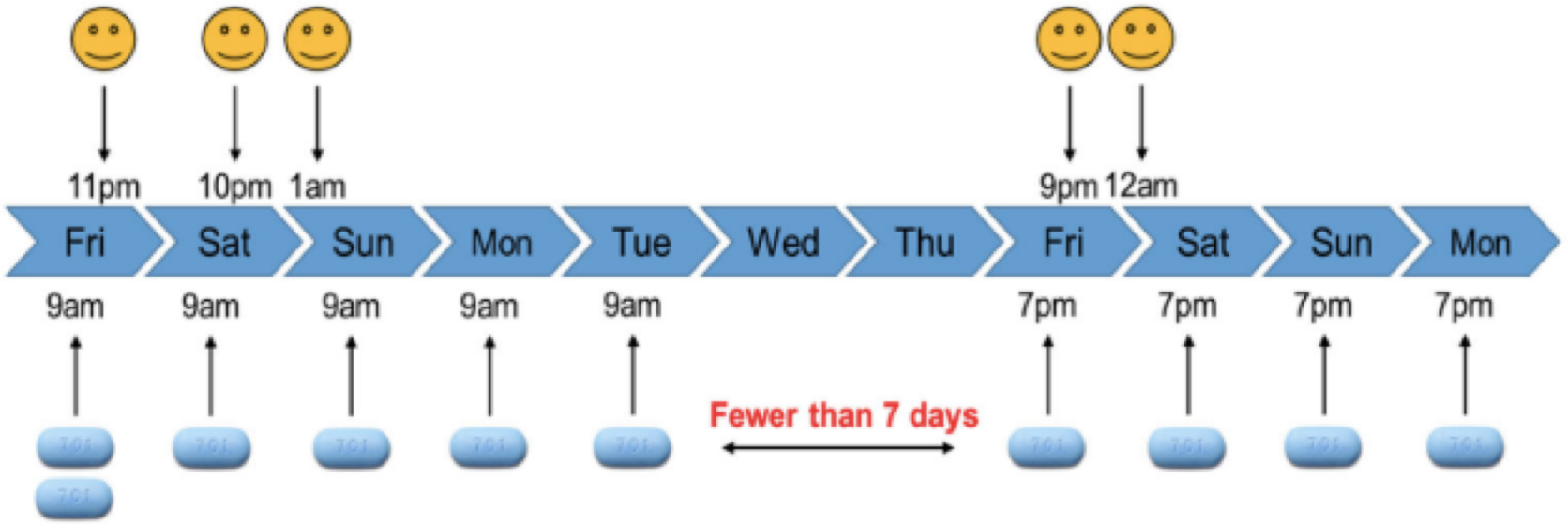
Example 2: Multiple sex episodes.
Continue 1 PrEP tablet every 24 hours until 2 days after last "sex day."



Saberi P. and Scott HM. *J Gen Intern Med.* 2019

How is 2-1-1 done?

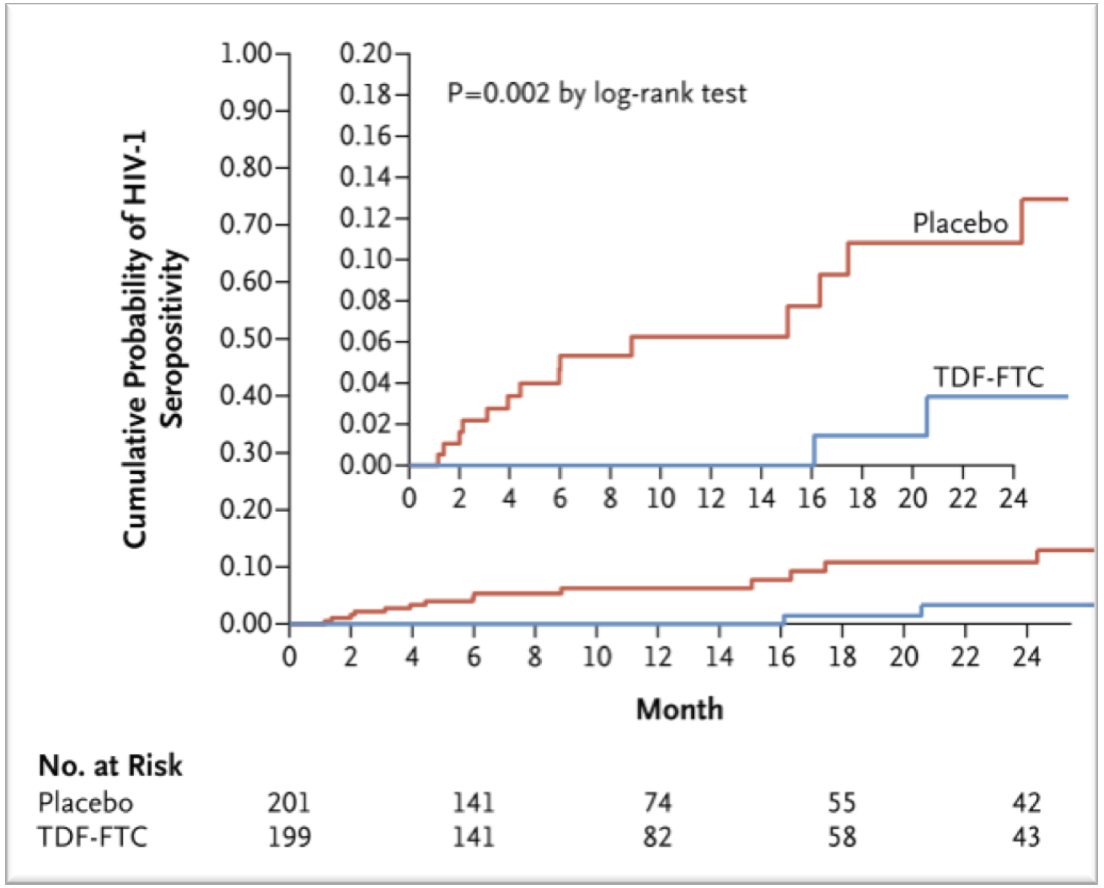
Example 3: Multiple sex episodes in one week.
If there are <7 days between end of one on-demand dosing period and beginning of another, take one single PrEP tablet to restart.
If there are ≥7 since last PrEP dose, start again with 2 PrEP tablets.



Saberi P. and Scott HM. *J Gen Intern Med.* 2019

IPERGAY Findings

- RCT in France and Canada of MSM and TGW randomized to on-demand PrEP vs. Placebo
- Median # of pills per month: 15
- 16 new HIV infections
  - TDF-FTC: 2 (0.91/100 PY)
  - Placebo: 14 (6.60/100 PY
- Relative risk reduction of 86% (95% CI, 40-98; P=0.002)
- NNT 17



Molina et al. *New Engl J Med.* 2015

Efficacy, safety, and effect on sexual behaviour of on-demand pre-exposure prophylaxis for HIV in men who have sex with men: an observational cohort study

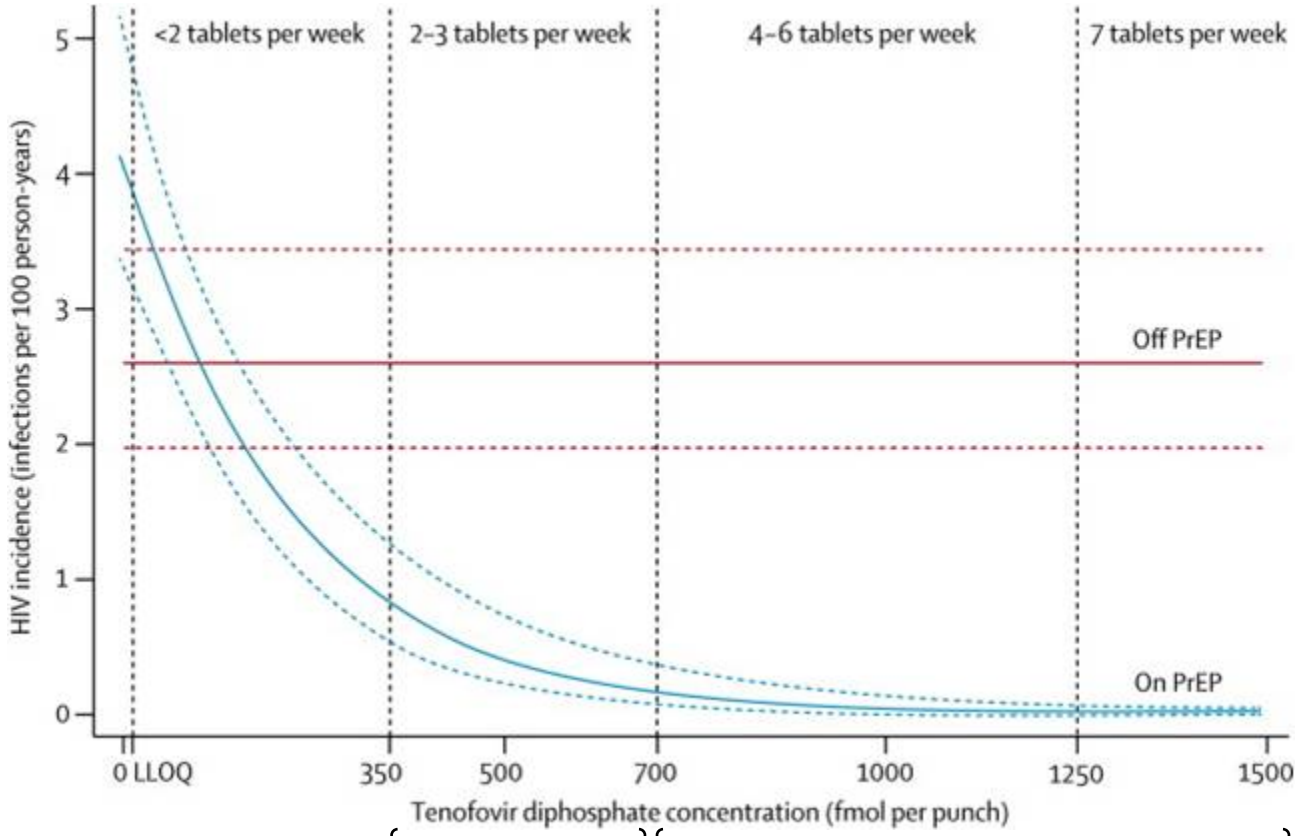
*Jean-Michel Molina, Isabelle Charreau, Bruno Spire, Laurent Cotte, Julie Chas, Catherine Capitant, Cecile Tremblay, Daniela Rojas-Castro, Eric Cua, Armelle Pasquet, Camille Bernaud, Claire Pintado, Constance Delaugerre, Luis Sagaon-Teyssier, Soizic Le Mestre, Christian Chidiac, Gilles Pialoux, Diane Ponscarme, Julien Fonsart, David Thompson, Mark A Wainberg†, Veronique Doré, Laurence Meyer, for the ANRS IPERGAY Study Group**

- Open-label extension of the IPERGAY trial
- All participants were offered on-demand PrEP (n=361)
- Median duration of follow-up: 18.4 months
- Only 2 transgender women (2/361); all other participants were cis men

Findings

- Low incidence of HIV infections
  - On-demand: 0.19/100 PY
  - Placebo: 6.6/100 PY
  - RRR: 97% (CI, 81-100)
- Similar safety data as randomized trial

TDF/FTC PrEP efficacy and Adherence (iPrEx)



{ 2-3 doses wk } { 4 doses and more/week }

Grant RM et al. Lancet Inf. Disease. 2014

What about less frequent sex?

- Post-hoc analyses of 270 participants (134 person-years) who had periods of less frequent sex (15 pills or fewer per month) and high PrEP adherence

	IPERGAY RCT	2017 Sub-Analyses
Median # of sex acts/month	10	5
Median # of pills taken/month	15	9.5

	Person-years	# HIV infections	HIV incidence rate/100 py (95% CI)	P
Placebo	64.8	6	9.3 (3.4-20.1)	
TDF/FTC	68.9	0	0.0 (0.0-5.4)	0.013

Antoni et al. Lancet HIV. 2020

Who can be offered on-demand PrEP?

	2-1-1 PrEP	Daily PrEP
Who can use it?	Only studied in MSM Small numbers of TGW who have sex with men (no frontal sex)	Anyone
Chronic HBV	Can trigger a flare	Can be used safely
Planning	Need to plan sex at least 2 hours in advance	No planning needed
“Forgiveness”	Not forgiving of missed doses	Forgiving of missed doses during the week

Slide credit: Scott, H. *2019 Ryan White HIV/AIDS Clinical Conference.*

What do you recommend?

a) No PrEP (*No, the patient should be given the option for taking PrEP given that he is MSM)*
b) Daily TDF/FTC (definitely an option)
c) On-demand TDF/FTC (likely effective if able to adhere to regimen)
d) Daily TAF/FTC (Yes, if willing to take daily, *on-demand has not been studied with TAF/FTC)*
e) On-demand TAF/FTC (*No, on-demand has not been studied with TAF/FTC)*

Case 3:

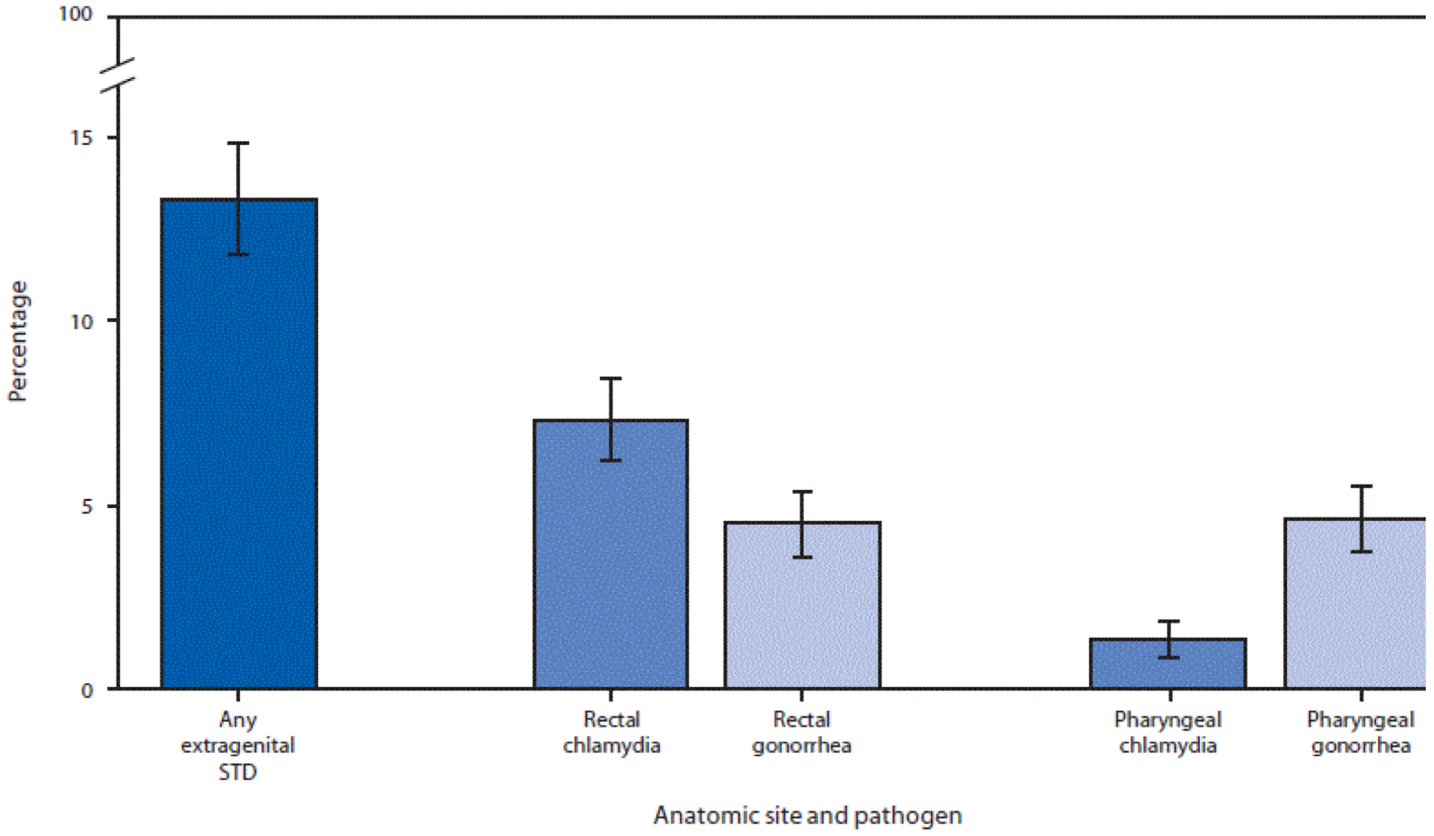
- 34 yo MSM presents for routine STI screening.
- He has a remote history of chlamydia and has no other prior STI history. He is asymptomatic at present and has had 2 new partners since his last visit 1 year ago. You order labs which return as follows:
- Syphilis EIA Negative
- HIV Ab/AG Non-reactive
- Urine GC PCR: Negative
- Urine CT PCR: Negative

Case Cont'd

- He messages you 1 week later and states that his most recent partner told him he recently tested positive for chlamydia. The patient denies any sexual activity since last testing but reports that he has had both receptive anal and oral intercourse with this partner. He continues to deny any symptoms at present.
- What (if any) additional testing would you order?

Extragenital Chlamydia and Gonorrhea Among Community Venue–Attending Men Who Have Sex with Men — Five Cities, United States, 2017

MMWR / April 12, 2019 / 68(14);321–325

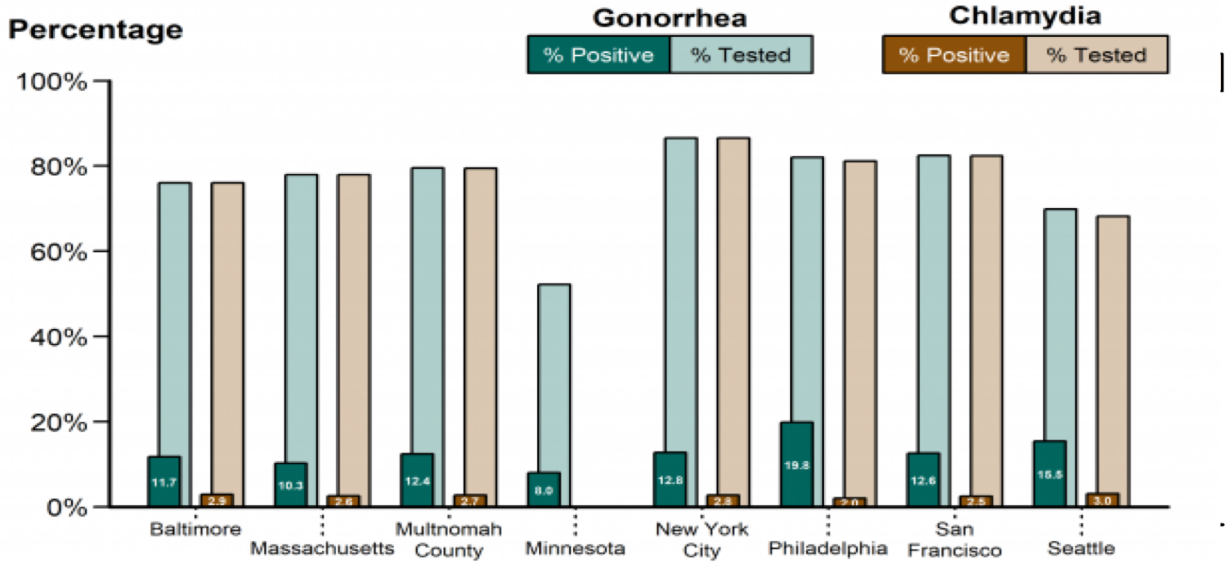


- 2371 eligible MSM screened at community sites in 5 US cities
- 34% had not been screened in prior yr- rates of STI no different

- Take home: Sexually active MSM should be screened at least annually for chlamydia and gonorrhea at all exposed anatomic sites; higher risk, every 3-6 months

GU and Extragenital GC/CT among MSM

Figure FF. Gonorrhea and Chlamydia — Proportion* of MSM STD Clinic Patients Tested and Testing Positive† for Pharyngeal Gonorrhea and Chlamydia by Jurisdiction, STD Surveillance Network (SSuN), 2018



* Results based on data obtained from unique patients with known sex of sex partners tested for pharyngeal gonorrhea (n=23,695) and for pharyngeal chlamydia (n=21,767) ≥1 time in 2018.

† Percent positive among those tested for pharyngeal gonorrhea or chlamydia.

NOTE: See section A2.2 in the Appendix for SSuN methods.

ACRONYMS: MSM = Gay, bisexual, and other men who have sex with men.

Association of HIV Preexposure Prophylaxis With Incidence of Sexually Transmitted Infections Among Individuals at High Risk of HIV Infection

JAMA. 2019;321(14):1380-1390. doi:10.1001/jama.2019.2947

Table 2. Incidence of Sexually Transmitted Infections During Follow-up Among Included Participants (N = 2981)

	No. of Infections	Person-Years of Follow-up (n = 3185.0)[a]	Incidence Rate per 100 Person-Years (95% CI)
All STIs	2928		91.9 (88.7-95.3)
Chlamydia	1434		45.0 (42.7-47.4)
Rectal[b]	1091		34.3 (32.3-36.3)
Urethral[b]	381		12.0 (10.8-13.2)
Pharyngeal[b]	127		4.0 (3.3-4.7)
Gonorrhea	1242		39.0 (36.9-41.2)
Rectal[b]	719		22.6 (21.0-24.3)
Urethral[b]	233		7.3 (6.4-8.3)
Pharyngeal[b]	629		19.7 (18.3-21.3)
Syphilis	252	3140.8	8.0 (7.1-9.0)
Site[b]			
Rectal infections	1810		56.8 (53.4-60.4)
Urethral infections	614		19.3 (17.4-21.3)
Pharyngeal infections	756		23.7 (22.0-25.6)
Age group,y[c]			
18-24 (n = 307)	161	186.1	86.5 (74.6-101.5)
25-29 (n = 634)	554	536.3	103.3 (94.9-112.1)
30-34 (n = 620)	733	684.4	107.1 (99.8-115.3)
35-39 (n = 482)	495	593.2	83.4 (76.4-91.2)
40-44 (n = 356)	354	432.2	81.9 (73.8-90.9)
45-49 (n = 437)	486	548.0	88.7 (81.2-97.1)
≥50 (n = 145)	145	204.7	70.8 (60.2-83.4)

Abbreviation: STI, sexually transmitted infection.

[a] Number of person-years indicated unless otherwise stated.

[b] Sum is greater than all STIs total as concurrent diagnosis of same infection at multiple anatomic sites was considered a single infection in the all STIs total.

[c] Subgroup analysis indicates all STIs.

- Overall incidence of STI 91/100person years
- PrEP use was associated with increased STI Risk, has not been consistently shown across trials
- In this study extragenital infections made up 74% of Chlamydia and 82% Gonococcal infections

Case Cont'd

- You obtain oropharyngeal and rectal NAAT for Chlamydia and Gonorrhea. The patient is diagnosed with rectal chlamydia and prescribed 1g of azithromycin.
- Three months later, he returned to clinic. He denied having receptive anal intercourse in the interim.
- A repeat rectal swab was collected per patient request, which came back positive for rectal chlamydia.
- How would you treat him?

Case 3 of persistent rectal chlamydia

A. Retreat with 1g of azithromycin
B. Doxycycline 100 mg BID for 7 days
C. Levofloxacin 500 mg once daily for 7 days
D. Erythromycin 500 mg four times a day for 7 days

Recommended Regimens
Azithromycin 1 g orally in a single dose OR **Doxycycline** 100 mg orally twice a day for 7 days

Alternative Regimens
Erythromycin base 500 mg orally four times a day for 7 days OR **Erythromycin ethylsuccinate** 800 mg orally four times a day for 7 days OR **Levofloxacin** 500 mg orally once daily for 7 days OR **Ofloxacin** 300 mg orally twice a day for 7 days

CDC 2015 Treatment Guidelines

Doxycycline may be more effective at treating rectal chlamydia than azithromycin

- Meta-analysis (2014) found much higher cure rates with doxycycline than azithromycin for rectal chlamydia:
  - Doxycycline: 99.6%
  - Azithromycin: 82.9%
  - Efficacy difference: 19.9%, CI: 11.4% to 28.3%

Kong et al. BMC Infect Dis. 2014

Rectal CT are common in women

- 6% of women who attend STI clinic who were tested for rectal chlamydia tested positive
- 68% of women who tested positive for urogenital chlamydia had concurrent rectal chlamydia
- 2.2% had rectal only positivity
- Reported anal intercourse was not associated with rectal chlamydia

Chandra et al. Sex Transm Infect. 2018

Treatment Effectiveness of Azithromycin and Doxycycline in Uncomplicated Rectal and Vaginal *Chlamydia trachomatis* Infections in Women: A Multicenter Observational Study (FemCure)

Nicole H. T. M. Dukers-Muijrers,[1,2] Petra F. G. Wolffs,[2] Henry de Vries,[3,4,5] Hannelore M. Götz,[5,6,7] Titia Heijman,[3] Sylvia Bruisten,[3,4] Lisanne Eppings,[1] Arjan Hogewoning,[3,4] Mieke Steenbakkers,[1] Mayk Lucchesi,[2] Maarten F. Schim van der Loeff,[3,4] and Christian J. P. A. Hoebe[1,2]

- Prospective multicenter cohort study
  - Doxycycline 100 mg twice daily for 7 days for women initially positive for rectal CT
  - Azithromycin 1g single dose in vaginally positive and rectally untested or rectally negative
- Microbiological cure for rectal infections:
  - Doxycycline: 95.5%
  - Azithromycin: 78.5%
- Microbiological cure for vaginal infections:
  - Doxycycline: 95.4%
  - Azithromycin: 93.5%

Doxycycline may be more effective than azithromycin in treating rectal CT in women.

Clinical Considerations

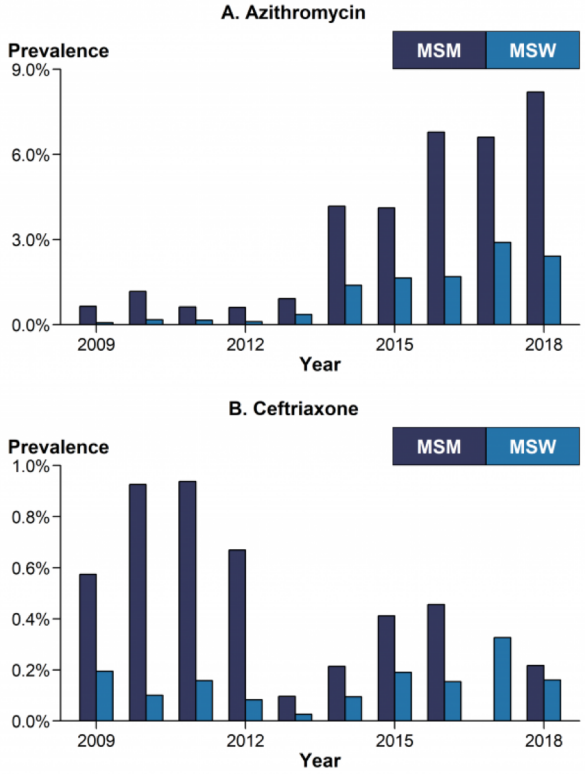
- Azithromycin:
  - 1 dose only
  - Easier to do expedited partner treatment
  - May take during pregnancy
  - Effective for genital CT
- Doxycycline:
  - 7 day treatment, need to assess for adherence issues
  - SE: photosensitivity, GI side effects
  - Contraindicated in pregnancy
  - May be more effective at treating rectal CT

Case of persistent rectal chlamydia

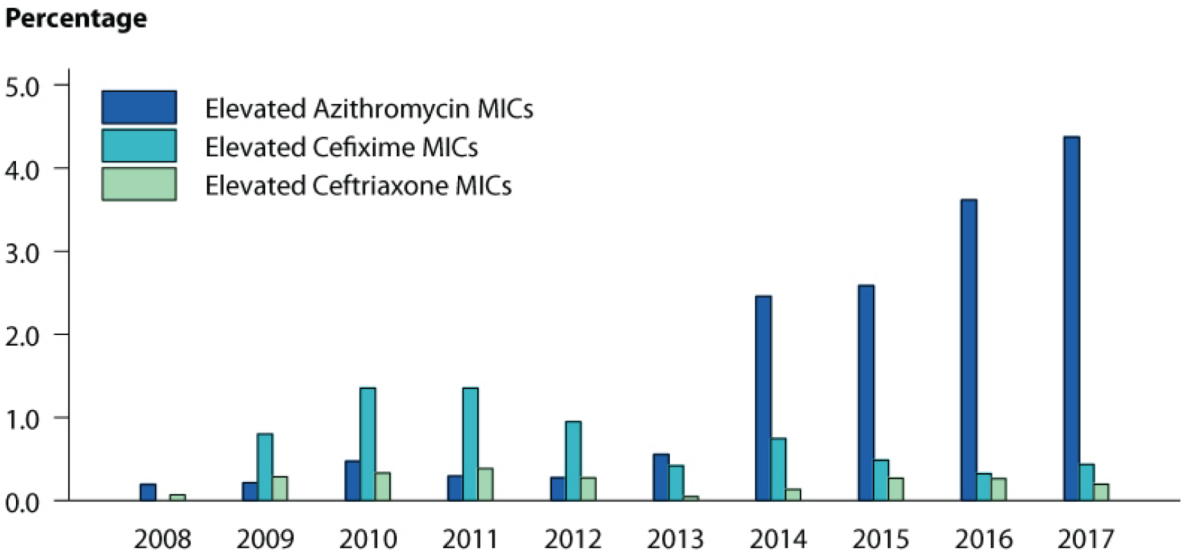
A. Retreat with 1g of azithromycin
B. Doxycycline 100 mg BID for 7 days
C. Levofloxacin 500 mg once daily for 7 days
D. Erythromycin 500 mg four times a day for 7 days

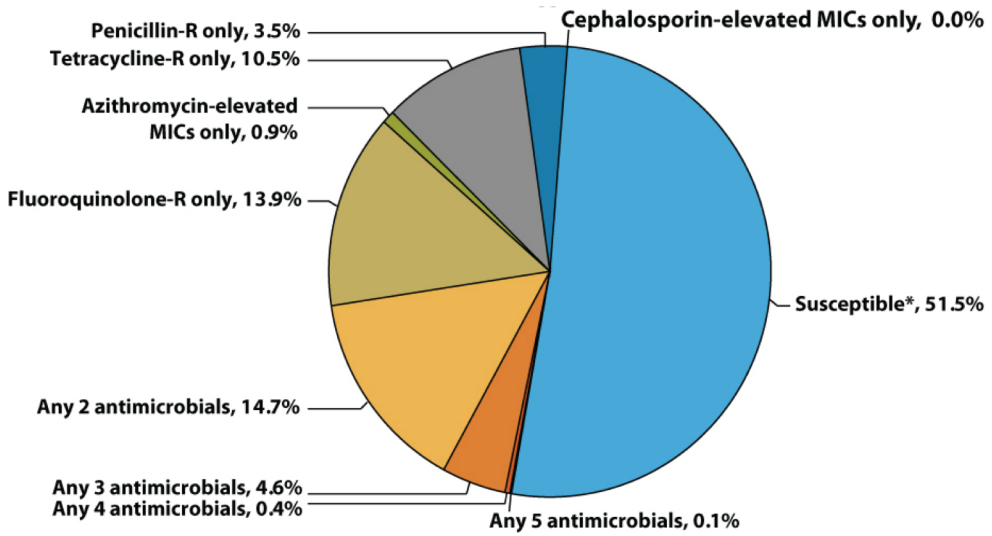
Gonococcal Resistance

Figure CC. *Neisseria gonorrhoeae* — Percentage of Urethral Isolates with Elevated Minimum Inhibitory Concentrations (MICs) to Azithromycin* and Ceftriaxone† by Sex and Sex of Sex Partners, Gonococcal Isolate Surveillance Project (GISP), 2009–2018



* Elevated Azithromycin MIC: ≥2.0 µg/mL.
† Elevated Ceftriaxone MIC: ≥0.125 µg/mL.
ACRONYMS: MSM = Gay, bisexual, and other men who have sex with men; MSW = Men who have sex with women only.





Gonorrhea Treatment

- Uncomplicated GC infection of urethra, cervix, pharynx, rectum:
  - Preferred:
    - Ceftriaxone 250mg IM x 1
    - Azithromycin 1g PO x 1
  - Alternative: (not for pharyngeal infection)
    - Cefixime 400mg PO x 1
    - Azithromycin 1g PO x 1
  - Cephalosporin Allergy:
    - Gemifloxacin 320mg PO x 1 OR Gentamycin 240mg IM x 1 + Azithromycin 2g PO x 1
- Disseminated Infection:
  - Ceftriaxone 1g IM/IV q day, Azithromycin 1g- Treat for total of 7 days

Case 4: Non-gonococcal urethritis

- 36 yo man who has sex with women presents with a clear penile discharge and dysuria.
- Empirically treated with azithromycin 1000 mg and ceftriaxone 150 mg IM in clinic.
- Urine GC/CT NAAT collected, along with 4th generation HIV screening test and treponemal ab. All tests were negative.
- Patient returns a week later with persistent symptoms.
- How would you treat him?

How would you treat him?

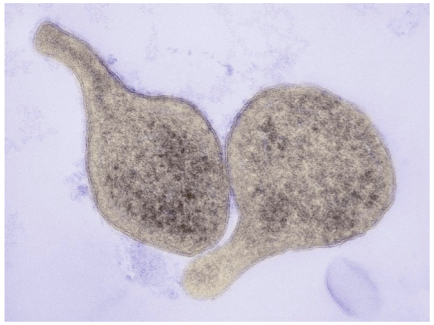
A) Treat with doxycycline 100 mg BID x 7 days
B) Treat with moxifloxacin 400 mg PO daily x 7 days
C) Get more testing
D) Treat with moxifloxacin 400 mg PO daily x 7 days and metronidazole 2 g PO for one dose

Non-gonococcal urethritis is the most common sexually transmitted syndrome in men

- Major causative organisms of urethritis in men:
  - C. trachomatis (32.7%)
  - N. gonorrhoeae (24.2%)
  - M. genitalium (22.2%)
  - T. vaginalis (5.2%)
  - Co-infection with C. trachomatis and M. genitalium (5.9%)
  - Co-infection with C. trachomatis and N. gonorrhoeae (5.9%)
- Other causative organisms (rare): HSV 1/2, adenovirus, Ureaplasma urealyticum, anaerobes

Gaydos et al. Sex Transm Infect. 2009

Mycoplasma Genitalium

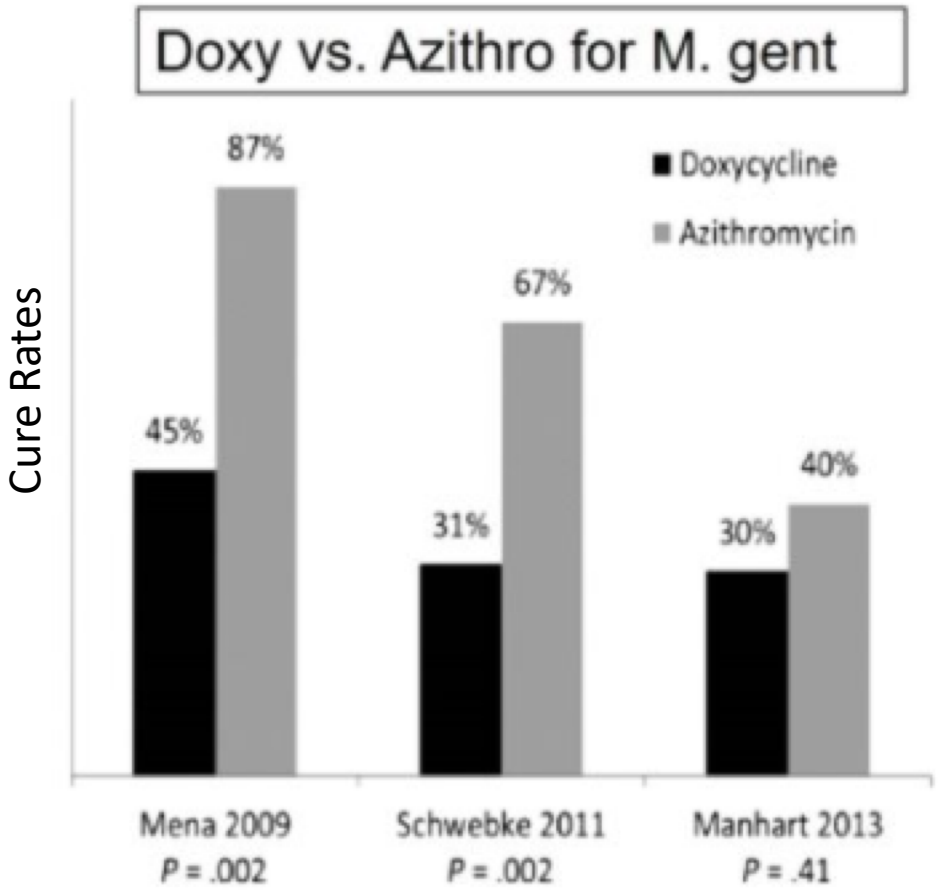


- One of the smallest known free-living organism; smallest genome of any species!
- Only pathogenic in the urogenital tract
- Men: discharge, dysuria, urethral stinging/itching, penile tip irritation, asymptomatic
- Women: cervicitis, pelvic inflammatory disease, infertility

Moi et al. BMC Infectious Diseases. 2015; Workowski et al. MMWR Recomm Rep. 2015
Image credit: https://images.app.goo.gl/7gkShz9d9RVWKXHD8

Diagnostic and Treatment Challenges

- Until 2019, there was no FDA-approved assay to detect M. Gent and macrolide resistance.
  - FDA approves Hologic's Aptima M. Gent assay (Jan 2019) for vaginal, endocervical, urethral and urine
- Increasing resistance to antibiotics
  - Single dose azithromycin can induce macrolide resistance in M. Gent.
    - Widespread use of azithromycin may explain the rise in M. Gent resistance
  - Low cure rates with doxycycline (20-40%). Preferred first-line for NGU if M gent unknown b/c:
    - 1) reduces organism load
    - 2) does not induce resistance



Moi et al. BMC Infectious Diseases. 2015; Mena et al. Clin Infect Dis. 2009; Schwebke et al. Clin Infect Dis. 2011; Manhart et al. Clin Infect Dis. 2013
Chart Credit: UCSF Grand Rounds, Stephanie Cohen, 2019
https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-first-test-aid-diagnosis-sexually-transmitted-infection-known-mycoplasma

NGU: A new treatment approach?

CDC 2015

Recommended Regimens

Azithromycin 1 g orally in a single dose
OR
Doxycycline 100 mg orally twice a day for 7 days

Alternative Regimens

Erythromycin base 500 mg orally four times a day for 7 days
OR
Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days
OR
Levofloxacin 500 mg orally once daily for 7 days
OR
Ofloxacin 300 mg orally twice a day for 7 days

Modified: Cohen, S. UCSF Grand Rounds. 2019; Durukan et al. Clin Infect Dis. 2019

SFDPH STD Clinic 2019

- NGU/other syndromes: Doxy 100 mg BID x 7d
- NAAT for GC/CT/Mgen
- Mgen(+): Moxi 400 mg Qd x 7 days
- If moxi fails: Minocycline 100 mg BID x 14 days

Australian Protocol

- NGU/cervicitis/PID/proctitis/contact to MG: doxy 100 mg BID x 7 d
- NAAT for GC/CT/Mgen & macrolide resistance mutation (MSM) assay
- Mgen+/MRM+: Moxi 400 mg qd x 7 days
- Mgen+/MRM-: azithro 1g then 500 mg qd x 3d

Cure rates: Doxy/azithro: 95.4%; Doxi/Moxi: 92%

How would you treat him?

A) Treat with doxycycline 100 mg BID x 7 days
B) Treat with moxifloxacin 400 mg PO daily x 7 days
C) Get more testing, if positive for Mgen → tx with moxifloxacin
D) Treat with moxifloxacin 400 mg PO daily x 7 days and metronidazole 2 g PO for one dose

Follow-up and Management NGU:

- Treat partners
- If M. gent positive, obtain TOC >3 weeks after treatment
- If GC/CT+, screen for reinfection in 3 months
- If persistent, eval for possible reinfection, resistance or trichomonas
  - May treat pre-emptively with metronidazole 2g orally as a single dose or tinidazole 2g orally in a single dose

Workowski et al. MMWR. 2015

CDC STI Screening Recommendations (2015)

	Chlamydia	Gonorrhea	HIV	Syphilis	Trich	HBV	HCV**
Cis-Women	<25 or risk	<25 or risk	13-64yo	*	Hi Prev/risk	Hi Risk	Born 1945-65, Hi risk
Pregnant	<25 or risk	<25 or risk	All	Yes		HBsAg	Born 1945-65, Hi risk
MSW	*Hi Prev	*	13-64	*		Hi Risk	Born 1945-65, Hi risk
MSM	Q3-12mo	Q3-12mo	>q12mo*	Q3-12 mo		Yes	Born 1945-65, Hi risk
HIV+ M	Dx, q12mo	Dx, q12mo		Dx, 12 mo		HBsAg, cAb, sAb	Dx, q12mo MSM
HIV+ F	Dx, q12mo	Dx, q12mo		Dx, q12mo	Dx, q12mo	HBsAg, cAb, sAb	Dx
Adolescents	F- Yes, M-*hi Prev	F-Yes, M-*	13+	*			

*= consider in high prevalence settings **= USPSTF recommends screening all adults age 18-79

Thank you! Questions?