

Florida HEALTH

Updates on DoxyPEP

Andréa Sciberras, DO, AAHIVS, FACOI, FACP,
Medical Director,
Division of Disease Control and Health
Protection
Florida Department of Health

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Disclosure

Disclosure: There are no conflicts of interest or financial incentives

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The new “morning after pill” ????



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Case study

A 32-year-old man with well-controlled HIV presents for a routine follow-up visit. He is sexually active with other men and rarely uses condoms. He is asymptomatic today and has a normal physical examination. He had pharyngeal gonorrhea 3 months ago, for which he received intramuscular ceftriaxone. Routine STI testing today is negative aside from a newly positive treponemal antibody, with an RPR of 1:512. He is treated with IM penicillin. Would you recommend doxyPEP for STIs for him (i.e., 200 mg taken 24-72 hours after sex)?

- A. Yes
- B. Yes, but only if he has a detectable viral load
- C. No
- D. I don't know.

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Why now?

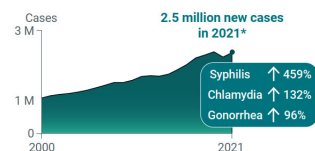
- Unchecked rise in reportable STIs
- Findings from multiple trials showing benefit
- Patients are asking about doxyPEP (and some are noting doxyPEP use on their dating app profiles)
- Many groups have already made recommendations for doxyPEP (e.g., California DOH)
- CDC has published considerations for doxyPEP

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Background: The Problem

STIs are climbing among all gender, racial and ethnic groups.



Groups Disproportionately Affected:

- Adolescents/Young Adults (aged 15-24 years)
- Pregnant individuals
- Individuals belonging to certain ethnic and racial minority groups
- Use of opioids and other drugs is linked to increased risk of STIs.
- Young adults who reported drug use in the past 12 months were **3x** more likely to get an STI.

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Question

In the state of Florida, which group has had the highest rate of syphilis transmission between 2018 and 2022?

- A. Men who have sex with men
- B. Heterosexual men
- C. Females

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What is Doxycycline?

- Belongs to tetracycline antibiotics class in use since 1940s. Doxycycline was introduced in 1967
- Some of many uses include: treatment of chlamydia, syphilis, M. genitalium, anthrax, some MRSA, Lyme and other rickettsial infections, treat acne, and to prevent malaria
- Generally, well tolerated and has a good safety profile even for those with renal failure/insufficiency.
- Known to have few drug-drug interactions.
- Affordable. According to NCSD (2023), doxycycline is approximately \$.06 per each 100 mg pill under 340B and \$.08/pill with a GoodRX card

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CDC 2019 | National Academies of Sciences, Engineering, and Medicine 2020 | Luetkemeyer et al. 2023 | NCSD 2023

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What is DoxyPEP?

- **Post-exposure preventative treatment for syphilis, chlamydia, and some* strains of gonorrhea.**
- DoxyPEP is used for:
 - Persons assigned male at birth, and
 - Have been diagnosed with at least one bacterial STI (i.e., chlamydia, gonorrhea, syphilis) in the last 12 months, and
 - Have had condomless oral and/or anal sexual contact with at least one individual assigned male at birth in the last 12 months

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How is DoxyPEP taken?



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How is DoxyPEP taken?

- 3 – take within 3 days/72 hours of exposure/condomless sexual intercourse (sooner the better)
- 2 – take 2 tablets of doxycycline (monohydrate or hyclate) 100mg
- 1- Take 1 dose
 - no more than 1 dose every 24 hours

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Considerations & Precautions

- May decrease effectiveness of hormonal contraceptives
- Should be avoided during pregnancy or if breast/chest feeding
- Avoid use in children
- Avoid taking with calcium containing supplements, antacids, multivitamins or foods like dairy

Possible Adverse Effects

- GI symptoms
- Pill esophagitis
- Photosensitivity
- Skin reactions
- Vaginal yeast infections

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Mayo Clinic 2023

DoxyPEP Concerns

1. **Antibiotic resistance**
 1. Especially in areas with overusage
2. **Changes in microbial flora**
3. Returning for follow-up – false sense of “free of infection”
4. Clinic-hopping
5. Sexual assault victims
6. Safety of 1 time dose in those who may be pregnant?
7. Access in rural areas, funding/costs, provider willingness, stigmas, access for others who are not MSM, etc.

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Old Medication, New Tool

Studies on use of doxycycline for STI post-exposure prophylaxis



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IPERGAY (France)

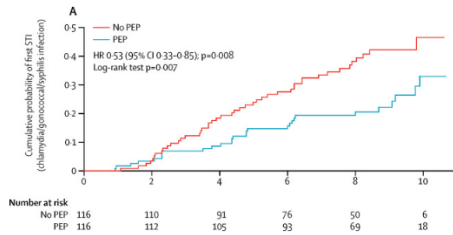
- Open-label randomized study focused on MSM taking HIV PrEP in France
- Participants (n=232) were randomly assigned 1:1 to doxyPEP or no PEP groups
- Limited to 3 doses of 200mg doxycycline per week
- STI testing every 2 months over 10 months for GC, CT and syphilis

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Molina et al. 2018 | Luetkemeyer et al. 2023

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IPERGAY



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Molina et al. 2018

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IPERGAY

- 70% reduction in chlamydia
- 73% reduction in syphilis
- No reduction in gonorrhea
 - Tetracycline resistance in gonorrhea is more prevalent in France (56% vs. 20% in the USA)
- GI symptoms reported by 53% of participants in doxyPEP group vs. 41% in the no PEP group
- High initial adherence to PEP
- Did not look at antibiotic resistance for non-STI organisms and obtained few GC and CT strains for antibiotic susceptibility
- Did not study *T. pallidum* strains for possible resistance mutations

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Molina et al. 2018

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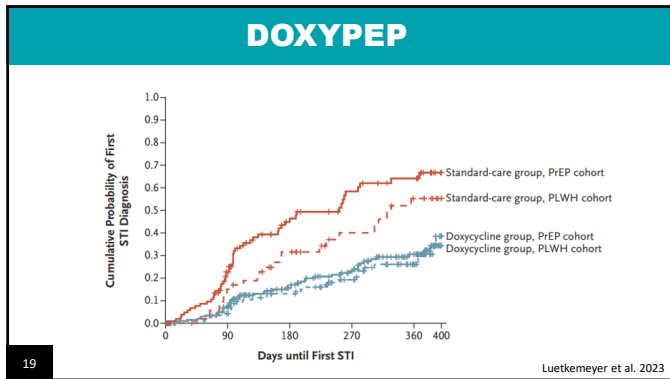
DOXYPEP (USA)

- Study in San Francisco focused on MSM and those assigned male at birth either taking HIV PrEP or living with HIV **and** have had an STI in the past year
- Open-label, randomized participants (n=501) 2:1 to take 200mg doxycycline within 72 hours after sexual encounter or receive standard care (no doxycycline)
- Could take medication daily but no more than 1 dose within 24 hours
- Quarterly STI testing for GC, CT and TP over 12 months

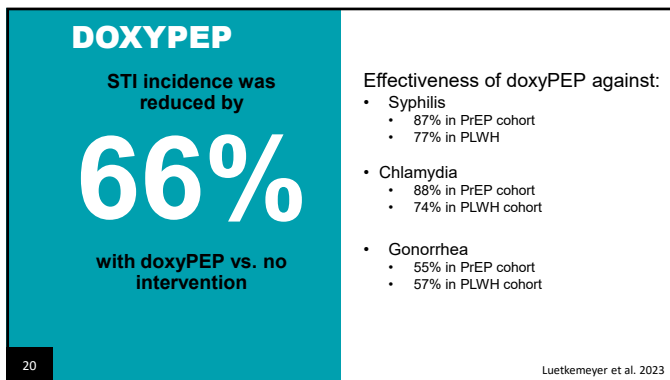
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Luetkemeyer et al. 2023

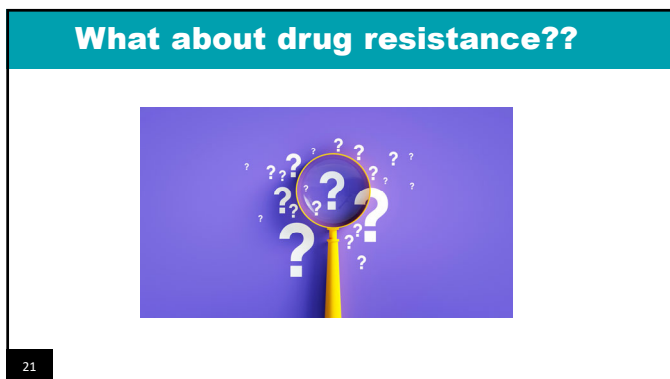
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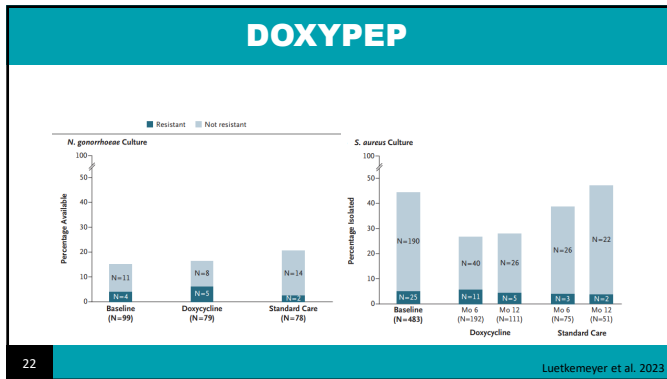
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DOXYPEP Study Limitations

- Measuring adherence was limited by patient recall
 - Adherence: 86% of participants reported consistent use within 72 hours of condomless sex and 71% reported never missing a dose
- Difficulty getting gonorrhea cultures (especially pharyngeal) and hence tetracycline susceptibility were available in only 17% of gonorrhea end points
- 27% baseline resistance to tetracyclines
- Enrollment of those assigned male at birth less than 5%
- Study conducted in 2 West Coast cities only

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Conclusions from DOXYPEP

“The effectiveness data provide evidence for doxy-PEP as an effective STI prevention for MSM with recent STIs and ongoing condomless sex, regardless of HIV serostatus.”

24 Luetkemeyer et al. 2023

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DOXYVAC (France)

- Open-label, randomized study in France looked at MSM on PrEP for over 6 months, that had an STI in the past 12 months
- Participants (n=332) were randomized to receive:
 - doxyPEP or no PEP (2:1)
 - 2 shots of meningococcal B vaccine or no vaccine (1:1)
- STI testing was performed every 3 months (GC/CT/MG PCR & TP serology) for up to 12 months
- Enrollment of new participants stopped 7 months early because an unblinded analysis pointed to significant effectiveness of both interventions; offer both doxyPEP and 4CMenB vaccine to all eligible

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Molina et al. 2023 (CROI)

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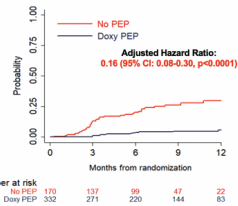
DOXYVAC

Doxycycline PEP Time to First CT or Syphilis Infection

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

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

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



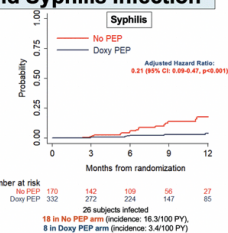
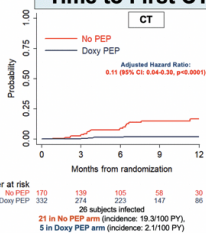
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Molina et al. 2023 (CROI)

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DOXYVAC

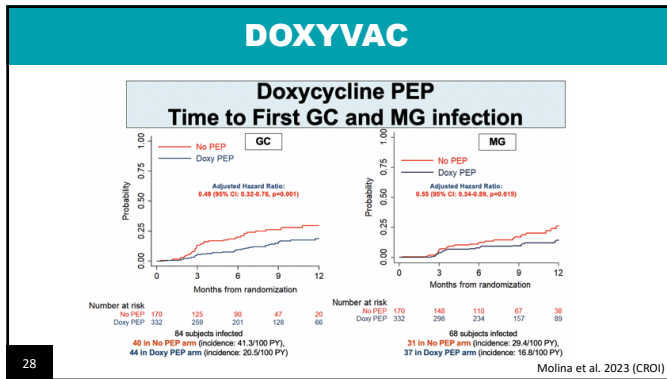
Doxycycline PEP Time to First CT and Syphilis Infection



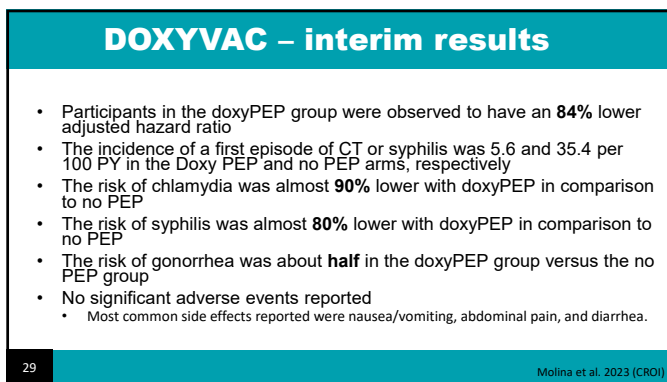
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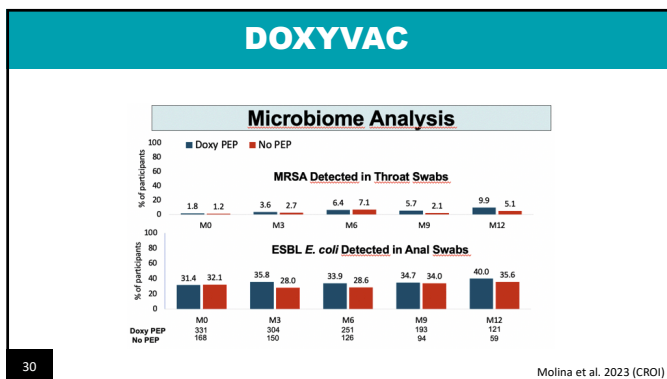
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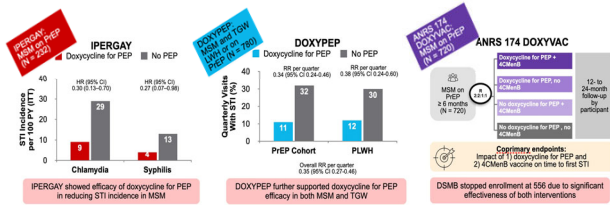


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3 Studies Supporting the Use of DoxyPEP



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True/False

There was a statistically significant difference in gastrointestinal adverse events amongst the DoxyPEP and no PEP groups in all 3 studies.

- A. True
B. False

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What about persons assigned female at birth?



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dPEP (Kenya)

- Open-label, randomized control trial in Kenya focusing on cisgender women on PrEP
- Participants (n=449) were randomized 1:1 to doxyPEP or no doxyPEP
 - Taking 200 mg of doxycycline hyclate within 72 hours of condomless sex
 - Contraception was not required
- Tested quarterly for STIs over 12 months of follow-up
- 18% had an STI at baseline
 - 100% of gonorrhea cases found at baseline were doxycycline-resistant
- Adherence measured via weekly SMS survey

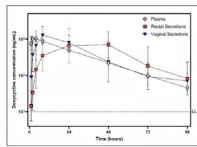
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Stewart et al. 2023 (CROI)

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dPEP

Mucosal Doxycycline Concentrations



Minimum Inhibitory Concentrations (MIC)
 At gonorrhea (NG) MIC = 200 ng/mL, CDC Antimicrob Resist Surv Test
 T penicillin (TP) MIC₅₀ = 100 ng/mL, Remington Antimicrob Agents Chemother 2020
 C doxycycline (C) MIC₅₀ = 14 ng/mL, Zhong Shi Fen 2015

	C doxycycline		T penicillin		N gonorrhea	
	Time	C ₅₀ * >4x MIC	Time	C ₅₀ * >4x MIC	Time	C ₅₀ * >4x MIC
Plasma	15x	44x	10x	32x	4x	3x
Rectal Secretions	11x	62x	7x	51x	3x	NA
Vaginal Secretions	20x	45x	12x	38x	5x	11x

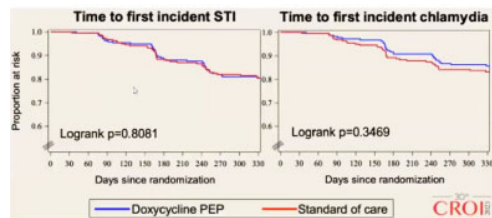
*Fold above MIC

Haaland CROI 2023, Abstract 118

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dPEP



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Stewart et al. 2023 (CROI)

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dPEP - Results

Results:

- No significant reduction in STIs
- Only 1 case of syphilis (but unknown how many were exposed)

Adherence:

- Weekly SMS surveys had an 81% response rate
- 78% of participants reported taking doxyPEP "at least as many days they had sex."
- Only 44% had detectable doxycycline in hair samples in a random subsample of 50 participants.

Possible explanations according to investigator:

- Poor adherence
- Anatomical differences (but confounded by data showing high levels in vaginal mucosa)
- Antibiotic resistance variations

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Stewart et al. 2023 (CROI)

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dPEP – Adherence Issues

High Self Reported adherence

Quarterly surveys

- 77% (579/755) coverage of last sexual exposure

Timeline follow-back calendar

- In 72.8% of the quarterly surveys, >80% of sexual acts were covered

Weekly SMS

- 64% (134/211) participants reported full coverage in at least 80% of weeks
- 78% of weekly SMS reported full coverage

Doxy Hair testing: 44% assigned to doxy-PEP never had doxycycline detected

Results: Hair drug testing

- In a randomly selected subset of 50 participants assigned to doxycycline PEP
 - 56.0% (28/50) of participants had doxycycline detected at least once
 - 29.0% (58/200) of all quarterly visits had doxycycline detected,
 - 32.6% (58/178) when medication holds excluded
- 6.7% (3/45) of enrollment visits had doxycycline detected
- 5.1% (2/39) of follow up visits among SOC group had doxycycline detected



Stewart et al dPEP ISSTD 7 2023 23

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dPEP Limitations

- Did not look specifically at syphilis (only 1 case out of 449, but unknown how many may have been exposed)
- Follow-up was short, not past 12 months
- Data on antibiotic resistance and how microbiome might be affected is limited
- Concluded that not enough information for value in cisgender women and adherence was a **HUGE** issue in the dPEP study

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Molina et al. 2018 | Luetkemeyer et al. 2023 | Molina et al. 2023 (CROI) | Stewart et al. 2023 (CROI) | CDC 2023

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Addressing overall DoxyPEP concerns

- Antimicrobial Resistance
 - No significant increase in gonorrhea AMR nor *Staphylococcus aureus* TCN-resistance in DOXYPEP.
 - High-level GC Resistance in DOXYVAC already but no increase in TCN-resistance in *S. aureus*
- Microbiome disruption
 - DOXYVAC without significant changes in *E. coli*, used as a marker for gut microbiome
- Long-term data are not yet available

Luetkemeyer et al. NEJM 2023
Molina et al., CROI 2023

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DoxyPEP summary

- Doxycycline as post-exposure prophylaxis for syphilis and chlamydia is highly effective
- DoxyPEP is safe
- Long term implications for antimicrobial resistance and gut microbiome are unknown, although short term data are reassuring
- More data are needed for effectiveness in persons assigned female at birth

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Syphilis

STI Treatment

Chlamydia

Doxy

M. genitalium

gonorrhea

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Current news...

- California Department of Public Health:
 - Recently has recommended the use of doxyPEP in high risk groups (MSM and those assigned male at birth) who have had an STI in the past year, given the high rates observed in the state.
 - **They have also recommended offering doxyPEP via shared decision-making to all non-pregnant individuals at high risk for STIs and to those requesting doxyPEP, even if they have not disclosed their risk status or had an STI in the past.**
- The CDC has released considerations for doxyPEP as an STI prevention strategy, and is currently awaiting public input on guidance measures at this time.

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Contact Information



Andréa Sciberras, DO, AAHIVS, FACOI, FACP,
Medical Director,
Division of Disease Control and Health
Protection,
Florida Department of Health
Andrea.sciberras@flhealth.gov
(850) 756-2283

Thank you!!

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Abbreviations

- CT= Chlamydia
- GC = Gonorrhea
- HIV= Human Immunodeficiency Virus
- MG= M. genitalium
- TP = Syphilis
- Doxy= Doxycycline
- PEP= post-exposure prophylaxis
- MSM = men who have sex with men
- DSMB=Data and Safety Monitoring Board

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