Prevention of STIs among People at Risk for HIV

Jean-Michel Molina, MD
University of Paris Cité, France
Washington DC, USA, June 5, 2023
### STI incidence before/after PrEP in MSM

- 1378 participants of the PrEPX study in Australia with pre-enrollment testing data
- Mean follow-up of 1.1 years

<table>
<thead>
<tr>
<th></th>
<th>STI incidence 1 year before per 100 PY</th>
<th>STI incidence post entry per 100 PY</th>
<th>Incidence rate ratio (IRR) (95% CI)</th>
<th>Adjusted IRR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>69.5</td>
<td>98.4</td>
<td>1.41 (1.29–1.56)</td>
<td>1.12 (1.02–1.23)</td>
</tr>
<tr>
<td>PrEP-experienced</td>
<td>92.4</td>
<td>104.1</td>
<td>1.13 (0.99–1.28)</td>
<td>1.05 (0.92–1.19)</td>
</tr>
<tr>
<td>(n=541)</td>
<td></td>
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</tr>
<tr>
<td>PrEP-naive</td>
<td>55.1</td>
<td>94.2</td>
<td>1.71 (1.49–1.96)</td>
<td>1.21 (1.06–1.39)</td>
</tr>
<tr>
<td>(n=837)</td>
<td></td>
<td></td>
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</tbody>
</table>

*Adjusted for testing frequency

PY, person-years

How to contain the STI Epidemic?

- A, B and C: Promotion of condom use
  - Counselling and behavioural changes
- Test and Treat
  - Frequent testing for STIs MSM on PrEP and immediate treatment
- Partner notification and treatment
- Antibiotic prophylaxis
- Vaccines
  - For viral STIs (hepatitis A and B, HPV, MPox)
  - For bacterial STIs when available (gonorrhea, chlamydia, syphilis)
    - Case-control studies suggest 4CMenB vaccine could reduce gonorrhoeae incidence
Doxycycline PEP in MSM

Randomized open-label trial

- HIV-negative MSM on PrEP
- Enrolled in the ANRS IPERGAY open-label extension study
- No contra-indication to Doxy

On Demand PEP with doxycycline (200 mg, within 24-72h after sex)  
N=116

No PEP  
N=116

* ≤ 6 pills/week to limit antibiotic exposure: use of a median of 6.8 pills/month per patient

- Visits at baseline and every two months with serologic assays for HIV and syphilis and PCR assays for CT and NG in urine samples, anal and throat swabs

PCR, Polymerase chain reaction; CT, chlamydia trachomatis; NG, Neisseria gonorrhoeae

Why Testing Doxycycline PEP?

- No known resistance to doxycycline in *C. trachomatis* and *T. pallidum*
- Doxycycline PEP successfully used for prevention of Lyme disease and Leptospirosis (Nadelman, NEJM 2001; Takafuji, NEJM 1984)
- Limited use of doxycycline in France for the treatment of bacterial infections, mostly used for acnea and malaria prophylaxis
- *N. gonorrhoeae* in France already resistant to tetracycline (65% in 2020-21, 20-30% high level with tetM acquisition)
A TRIAL OF MINOCYCLINE GIVEN AFTER EXPOSURE TO PREVENT GONORRHEA

William O. Harrison, M.D., Richard R. Hooper, M.D., Paul J. Wiesner, M.D., Axel F. Campbell, M.D., Walter W. Karney, M.D., Gladys H. Reynolds, Ph.D., Oscar G. Jones, B.S., and King K. Holmes, M.D., Ph.D.

- 1089 men were given oral minocycline (200 mg) or placebo after sex (median: 8 h)
- At sea, gonorrhea in 57/565 (10%) with placebo and 24/515 (4.7%) with PEP (p<0.001)
- Isolates from patients given PEP were more resistant to tetracycllin vs. those given placebo
- Efficacy of PEP related to NG MIC
- High failure rate with minocycline treatment: 65%
- "Limited effectiveness as a public health measure"
Median follow-up of 8.7 months (IQR: 7.8-9.7): 73 subjects infected

45 in No PEP arm (incidence: 69.7 per 100 PY), 28 in PEP arm (incidence: 37.7 per 100 PY)

Hazard Ratio: 0.53 (95% CI: 0.33-0.85, p=0.008)
Incidence of First Episode of Chlamydia

- Median follow-up of 8.7 months (IQR: 7.8–9.7): 28 subjects infected
- **21 in no PEP arm** (incidence: 28.6/100 PY), **7 in PEP arm** (incidence: 8.7/100 PY)
- Hazard Ratio: 0.30 (95% CI: 0.13-0.70, p=0.006)

Incidence of First Episode of Syphilis

- Median follow-up of 8.7 months (IQR: 7.8-9.7): 13 subjects infected
- **10 in no PEP arm** (incidence: 12.9 / 100 PY), **3 in PEP arm** (incidence: 3.7/100 PY)
- **Hazard Ratio:** 0.27 (95% CI: 0.07–0.98, p<0.05)

## Sites of *N. gonorrhoeae* Infection

<table>
<thead>
<tr>
<th>SITE PCR +</th>
<th>PEP Doxy</th>
<th>No PEP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anus</td>
<td>11</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Throat</td>
<td>15</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td>1</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td><strong>Total sites</strong></td>
<td><strong>27</strong></td>
<td><strong>38</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Total infections</strong></td>
<td><strong>27</strong></td>
<td><strong>30</strong></td>
<td><strong>0.63</strong></td>
</tr>
<tr>
<td><strong>Infections per 100 py</strong></td>
<td><strong>32.6</strong></td>
<td><strong>37.3</strong></td>
<td></td>
</tr>
</tbody>
</table>

Molina et al. Lancet ID 2018
Co-Chairs Choice

Doxycycline post-exposure prophylaxis for prevention of STIs among MSM and TGW who are living with HIV or on PrEP

Annie Luetkemeyer, Julie Dombrowski, Stephanie Cohen, Deborah Donnell, Cole Grabow, Clare Brown, Cheryl Malinski, Rodney Perkins, Melody Nasser, Carolina Lopez, Susan Buchbinder, Hyman Scott, Edwin Charlebois, Diane Havlir, Olusegun Soge, Connie Celum on behalf of the DoxyPEP Study Team
**Intervention:** Open label doxycycline 200mg taken as PEP within 72 hours after condomless sexual contact

*Maximum of 200 mg every 24 hours*

**Inclusion criteria:**
- Male sex at birth
- Living with HIV or on PrEP
- ≥ 1 STI in past 12 months
- Condomless sex with ≥ 1 male partner in past 12 months

**STI Testing:** Quarterly 3 site GC/CT testing + RPR, GC culture before treatment

**Sites:** San Francisco & Seattle HIV & STI clinics

**Detect a 50% reduction of STIs/quarter with doxyPEP**

Stopping boundaries for effectiveness: $\alpha < 0.025$ for both cohorts

DSMB recommended early discontinuation in May 2022 at first interim analysis
Primary Endpoint: STI incidence per quarter (501 pts enrolled)

**PrEP cohort**
- STI incidence:
  - Gonorrhea only: 31.9% (82/257)
  - Chlamydia only: 11.8% (36/305)
  - Syphilis only: 31.9% (82/257)
  - >=2 STIs: 10.7% (61/570)

**PLWH cohort**
- STI incidence:
  - Gonorrhea only: 30.5% (39/129)
  - Chlamydia only: 11.8% (36/305)
  - Syphilis only: 31.9% (82/257)
  - >=2 STIs: 10.7% (61/570)

**Reduction in STI incidence/quarter**

<table>
<thead>
<tr>
<th>Group</th>
<th>Risk Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PrEP</td>
<td>0.34 (0.24 - 0.46)</td>
</tr>
<tr>
<td>Living with HIV</td>
<td>0.38 (0.24 - 0.60)</td>
</tr>
<tr>
<td>Total</td>
<td>0.35 (0.27 - 0.46)</td>
</tr>
</tbody>
</table>

All p < 0.0001

Luetkemeyer et al NEJM 2023
**Individual STI incidence by study arm & cohort**

**Anatomic site**
- Urethral only
- Pharyngeal only
- Rectal only
- >=2 sites

**Reduction in each STI per quarter**

<table>
<thead>
<tr>
<th>STI</th>
<th>PrEP</th>
<th>PLWH</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC</td>
<td>0.45</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>(0.32 - 0.65)</td>
<td>(0.26 - 0.71)</td>
</tr>
<tr>
<td></td>
<td><em>p&lt;0.0001</em></td>
<td><em>p=0.001</em></td>
</tr>
<tr>
<td>CT</td>
<td>0.12</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td>(0.05 - 0.25)</td>
<td>(0.12 - 0.57)</td>
</tr>
<tr>
<td></td>
<td><em>p&lt;0.0001</em></td>
<td><em>p=0.0007</em></td>
</tr>
<tr>
<td>Syphilis</td>
<td>0.13</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>(0.03 - 0.59)</td>
<td>(0.04 - 1.29)</td>
</tr>
<tr>
<td></td>
<td><em>p=0.0084</em></td>
<td><em>p=0.095</em></td>
</tr>
</tbody>
</table>

Luetkemeyer et al NEJM 2023
Doxy PEP was safe & acceptable, with high adherence

- **AEs attributed to doxycycline PEP:**
  No grade 3+ adverse events, grade 2+ lab abnormalities, or SAEs

- **Tolerability and acceptability:**
  - 1.5% discontinued due to intolerance or participant preference
  - 88% reported doxycycline PEP was acceptable/very acceptable

- **Adherence:** Median 7.3 (IQR 1–10) sex acts per month, with 87% covered by doxycycline per self-report

- **Doxycycline use:** Median of 4 doses (800 mg) per month (IQR: 1-10)

*Based on mean difference between pills dispensed and returned for pill count*
Tetracycline resistance (TCN-R) in incident GC with culture data

- TCN-R similar in incident GC at baseline and on doxy-PEP
- Increased TCN-R in doxy-PEP vs. standard of care suggests doxy-PEP may be less protective against GC strains with existing TCN-R
- Limited by low number of GC samples with MIC results (56/320)
Doxy-PEP use vs STIs averted in a US Sexual Health Clinic

Doxy-PEP prescribing scenario

- **Prescribe doxy-PEP to:**
  - All people: 70%
  - All PLWHIV and PrEP users: 68%
  - PrEP users: 55%
  - Any STI: 49%
  - Rectal STI: 42%
  - Gonorrhea Dx: 29%
  - 2 STIs in past 12m: 23%
  - 2 STIs in past 6m: 19%
  - Syphilis Dx: 19%
  - Concurrent STIs: 15%

Proportion of all STIs averted by doxy-PEP

- Proportion of all individuals prescribed doxy-PEP

Traeger M, CROI 2023, Abs. 122
Multicenter, 2 x 2 factorial randomized, open-label, superiority, phase III trial (NCT04597424)

- Primary efficacy end-points: impact of DoxyPEP on time to a first episode of syphilis or chlamydia and impact of the 4CMenB vaccine on time to a first episode of *N. gonorrhoeae* infection.

- Sample size: based on vaccine effectiveness assuming no impact of Doxy on GC: 720 subjects needed for an HR: 0.70 (Estimated probability of a first GC episode over 18 months: 52%, power 85%, 18% lost to FU).

- Quaterly visits with PCR tests (Roche dual target Cobas) for GC/CT/MG (3 sites) and serology for TP

- Doxycycline monohydrate purchased from Arrow and 4CMenB vaccine purchased from GSK

Molina JM, CROI 2023
ANRS 174 DOXYVAC
Premature Study Discontinuation

- August 2022 DOXYPEP results: 65% reduction in STIs incidence (CT and syphilis ~ 80%; GC ~ 55%)
- September 2, 2022: DOXYVAC DSMB requested unblinded analysis on participants enrolled from 01/19/2021 to 07/15/2022
- Significant effectiveness of both interventions and DSMB recommended to:
  - stop enrollment of new participants
  - offer Doxy PEP and 4CMenB vaccine to all
- Recommendations endorsed by the scientific committee and ANRS

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)

Adjusted Hazard Ratio:
0.16 (95% CI: 0.08-0.30, $p<0.0001$)
Doxycycline PEP
Time to First GC infection

84 subjects infected

40 in No PEP arm (incidence: 41.3/100 PY),
44 in Doxy PEP arm (incidence: 20.5/100 PY)

Adjusted Hazard Ratio:
0.49 (95% CI: 0.32-0.76, p=0.001)
- 65 cultures available for resistance testing (15% of PCR positive samples)
- Tetracycline MICs determined by Etest
- Resistance using EUCAST 2023 breakpoints
  - Resistance: MIC > 0.5 mg/L
  - High level resistance: MIC > 8 mg/L

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Doxy PEP</th>
<th>No PEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>7</td>
<td>21</td>
<td>37</td>
</tr>
<tr>
<td>Susceptible</td>
<td>100</td>
<td>66.7</td>
<td>81.1</td>
</tr>
<tr>
<td>Resistant</td>
<td>0.0</td>
<td>33.3</td>
<td>18.9</td>
</tr>
<tr>
<td>High level</td>
<td></td>
<td>0.0</td>
<td>18.9</td>
</tr>
</tbody>
</table>
Doxycycline PEP for Prevention of STIs among Kenyan Women on HIV PrEP

- 1:1 open-label randomized trial of dPEP (200mg doxycycline) taken within 72 hours after sex
- N=449 women taking PrEP, aged 18-30 (median age: 24 years)
- Quarterly follow-up for 12 months in Kisumu, Kenya
### DPEP KENYA TRIAL RESULTS

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Endpoint</th>
<th>Total</th>
<th>PEP (N=224)</th>
<th>SOC (N=225)</th>
<th>RR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention to Treat</td>
<td>All STIs</td>
<td>109</td>
<td>50</td>
<td>59</td>
<td>0.88</td>
<td>0.60-1.29</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td>Chlamydia</td>
<td>85</td>
<td>35</td>
<td>50</td>
<td>0.73</td>
<td>0.47-1.13</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>Gonorrhea</td>
<td>31</td>
<td>19</td>
<td>12</td>
<td>1.64</td>
<td>0.78-3.47</td>
<td>0.19</td>
</tr>
</tbody>
</table>

#### Time to first incident STI

- **Doxycycline PEP**
- **Standard of care**

![Graph showing time to first incident STI](image)

Logrank p=0.8081

#### Time to first incident Chlamydia

- **Doxycycline PEP**
- **Standard of care**

![Graph showing time to first incident Chlamydia](image)

Logrank p=0.3469

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**No HIV infection, 1 syphilis**

- Genomic test for tetracycline R (tetM and tetC)
  - 100% (28/28) for Ng
  - 0% (0/66) for Ct

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**DoxyPEP self-reported adherence 78%**

Stewart J, CROI 2023, Abs. 121
**Doxycycline Concentrations following 200 mg SD**

![Graph showing doxycycline concentrations in plasma, rectal, and vaginal secretions over time.](image)

<table>
<thead>
<tr>
<th></th>
<th>Time above <em>C. trachomatis</em> MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>C</em>&lt;sub&gt;max&lt;/sub&gt;</td>
</tr>
<tr>
<td>Plasma</td>
<td>16x</td>
</tr>
<tr>
<td>Rectal Secretions</td>
<td>11x</td>
</tr>
<tr>
<td>Vaginal Secretions</td>
<td>20x</td>
</tr>
</tbody>
</table>

**Minimum Inhibitory Concentrations (MIC):**

* C. trachomatis MIC<sub>90</sub> = 64 ng/mL

Zheng *Sex Transm Dis* 2015

Mucosal doxycycline concentrations greater than in plasma
- Reach >10x *C. trachomatis* MIC
- Remain >4x *C. trachomatis* MIC up to 2 days after dosing

Haaland R et al. CROI 2023
DOXYVAC: 4CMenB Vaccine to Prevent Gonorrhoaeae

**Time to First GC Infection**

- 49 subjects infected
  - 32 in No Vaccine arm (incidence: 19.7/100 PY),
  - 17 in 4CMenB vaccine arm (incidence: 9.8/100 PY)

**Cumulative GC Infections**

- 90 GC infections
  - 54 in No Vaccine arm,
  - 36 in 4CMenB vaccine arm

**Adjusted Hazard Ratio:**

0.49 (95% CI: 0.27-0.88, p=0.016)

**Adjusted Incidence Rate Ratio:**

0.66 (95% CI: 0.43-1.00, p=0.052)

Number at risk:

<table>
<thead>
<tr>
<th></th>
<th>No Vaccine</th>
<th>4CMenB vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>245</td>
<td>208</td>
<td>150</td>
</tr>
<tr>
<td>91</td>
<td>102</td>
<td>49</td>
</tr>
<tr>
<td>49</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GC infections were considered from M3 visit (1 month after 2nd vaccine dose)

Molina JM, CROI 2023
PRESS RELEASE

ANRS DOXYVAC: final analysis may modify interim results of this trial assessing the effectiveness of meningococcal B vaccination in preventing gonococcal infections

ANRS | Emerging Infectious Diseases will commission an independent audit

Paris, May 15, 2023
The Primary Outcome was Positive
Was that Good Enough?

• Does a P value < 0.05 provide strong enough evidence? A P value of 0.05 carries a 5% risk of a false positive result.
  – To provide proof beyond reasonable doubt, P<0.001 is wise: P-value was 0.016

• What is the magnitude of the treatment benefit: 51% incidence reduction clinically relevant
  – but 95% Confidence interval: 0.27- 0.88, only 12% reduction ensured

• Is the primary outcome clinically important? Mostly asymptomatic infections

• Are secondary outcomes supportive? Cumulative GC infection rates not significant (20.1 vs 30.4/100 PY, p=0.052)

• Was the trial stopped too early?: Interim analysis with all available data: no significant difference
  – Quality and completeness of any interim database are inevitably imperfect
  – Investigators were too happy about the results…

• Will the trial be underpowered? When a trial is too small to detect modest treatment effects, findings might be inconclusive

• Results of a single trial should be confirmed by a second trial.
  – Results will hopefully guide ongoing trials

• Physicians have the final responsibility for accurately interpreting clinical trial results

Key Takeaway

- **Doxycycline PEP reduces STI incidence among MSM**
  - 3 studies have shown consistent reductions of chlamydia, syphilis and gonorrheae
  - Doxycycline PEP is well tolerated with high self-reported adherence
  - Evaluation of full impact on antibiotic resistance is underway (STIs, microbiome)
  - Identify people who will benefit the most from this intervention

- **Evidence of 4CMenB Vaccine efficacy to prevent gonorrhoeae still pending**

- **STI research should continue**
  - Scientific priority to meet 2030 WHO/UNAIDS targets: reduce incidence of HIV and STIs by 90%
Acknowledgments

Anne Luetkemeyer and Connie Celum
Jennell Stewart
Richard Halland
Ipergay and Doxyvac participants and study teams

AIDES: D. Michels
ANRS/MIE: V. Petrov, S. Lemestre, C. Birkle, Y. Yazdanpanah
Back-up Slides
Discrepancy between Interim and Final Results

• Last participant enrolled on September 19, 2023
• Participants asked to perform a last visit to be offered both interventions (scheduled until Feb 28, 2023)
• Monitoring completed April 20, 2023 and final results presented to the trial steering committee (follow-up increased from 9 to 14 months)
• Discrepancy between interim and final analysis for vaccination effectiveness
• Number of GC events increased from 49 to > 200….
• All cases individually reviewed to understand the discrepancy
• Interim analysis was flawed because a whole file with GC events was omitted from the interim analysis