Biomedical Prophylaxis of HIV and other STIs
A Change in Paradigm?

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Disclosures

Advisory boards: Gilead, Merck, ViiV, Sanofi

Research grants: Gilead
1.8 M Newly Diagnosed HIV-Infection in 2017
6,000 New Infections Every Day
More than 160,000 HIV Diagnoses in the WHO European Region in 2016

West 16%
≈ 26,000 cases
6.2 per 100,000 population

Centre 4%
≈ 5,800 cases
2.9 per 100,000 population

East 80%
≈ 128,000 cases
50.2 per 100,000 population

Proportion of New HIV Diagnoses by Country and Transmission (EU/EEA 2017)

- Croatia
- Hungary
- Slovakia
- Netherlands
- Czech Republic
- Slovenia
- Poland
- Austria
- Spain
- Ireland
- Malta
- Cyprus
- Greece
- United Kingdom
- Denmark

Sex between men

Heterosexual contact (males)

Heterosexual contact (females)

Injecting drug use

Other/undetermined

Note: Germany did not report data for 2017, 0 cases were reported by Liechtenstein
Prevention of HIV/AIDS without a Vaccine on the Horizon

- Abstain
- Be Faithful
- **Condoms**: 70-90% risk reduction of HIV sexual transmission (observational studies)
- **Circumcision in males**: 60% risk reduction of HIV transmission from women to men (2005 ANRS 12126 randomized trial)

**Drugs (Antiretrovirals) for HIV Prevention**
- Prevention of mother to child transmission: 67.5% reduction with AZT monotherapy (1994 ACTG 076 randomized trial)
- Post-Exposure Prophylaxis: 80% risk reduction with 4 weeks of AZT in health care workers (1997 case-control study USA/France)
- Treatment of HIV-infected individuals: 93% risk reduction of HIV transmission to HIV-uninfected partner (2011 RCT HPTN 052 trial)
- Pre-Exposure Prophylaxis (PrEP)
PrEP is Changing HIV Prevention

SWALLOW THIS

This pill is changing HIV prevention.
Take it once a day to stay HIV negative.

Is PrEP for you?

HARLEM UNITED
HarlemUnited.org/PrEP
What is PrEP?

- Use of antiretroviral drugs (Reverse Transcriptase Inhibitors) started before sexual exposure and continued after exposure to reduce the risk of HIV acquisition in high risk individuals.
- PrEP has shown efficacy in the macaque model.
- Antibiotic prophylaxis to prevent surgical site infections.
- Prevention of Malaria:
  - Mosquito-nets and repellents
  - Anti-malarial drugs: before exposure, during exposure and after the end of exposition.
iPrEx Study Design

Double-blinded, randomized, placebo-controlled trial

- HIV uninfected MSM at high risk of sexual acquisition of HIV
- High risk: in the 6 months prior to screening: anal sex with > 4 partners, STI, transactional sex, condomless anal sex
- HIV prevalence at screening: 8%
- Events driven trial: 85 events yield a power of 80% to reject the null hypothesis of efficacy of < 30% if the true efficacy is > 60%
- Rapid HIV testing at every 4 weeks visit, with drug dispensation and adherence counseling

After a median follow-up of 14 months, 100 subjects became infected, 36 in the TDF/FTC arm and 64 in the placebo arm:

44% reduction in the incidence of HIV (95% CI : 15-63, p=0.005)
Potential Benefits of On Demand PrEP

- Convenient dosing regimen which could improve adherence and overall effectiveness
- Clear guidance on how to start and stop PrEP
- Better safety due to lower drug exposure (kidneys, bones)
- Improved cost-effectiveness
- Easier diagnosis of breakthrough HIV-infection
- Lower risk of selecting drug resistance in case of HIV-infection
Effect of a Double Dose of oral TDF/FTC (-2h, + 24h)

Garcia-Lerma et al. Science Trans Med 2010, 14,14ra4
Study Design

Randomized Double-Blinded vs. Placebo then Open-Label Extension

- HIV-negative MSM
- Condomless anal sex with ≥ 2 partners in prior 6 months
- Creat. Clearance > 60 mL/mn
- HbS Ag negative

- Condoms, gels, tests for HIV (using 4th generation assays) and STIs, vaccinations for Hepatitis A and B, and peer counseling on risk reduction and adherence
- Follow-up every two months

Molina JM et al NEJM 2015
Partnership with the Community
IPERGAY : Sex-Driven iPrEP

- 2 tablets 2-24 hours before sex
- 1 tablet 24 hours later
- 1 tablet 48 hours after first intake

4 pills of TDF/FTC taken over 3 days to cover one sexual intercourse

On demand PrEP tells you How to Start and How to Stop PrEP
Mean follow-up of 12 months: 16 subjects infected (14 placebo, 2 in TDF/FTC)

Incidence: 6.6 /100 PY overall but 9.17 in Paris (and 2.45 in other cities)

86% relative reduction in the incidence of HIV-1 (95% CI : 40-98, p=0.002)

NNT to avert one HIV-infection: 18 (95% CI: 11-50)
HIV Incidence (mITT Analysis)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Follow-Up Pts-years</th>
<th>HIV Incidence per 100 Pts-years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>212</td>
<td>6.60 (3.60-11.1)</td>
</tr>
<tr>
<td>TDF/FTC (double-blind)</td>
<td>219</td>
<td>0.91 (0.11-3.30)</td>
</tr>
<tr>
<td>TDF/FTC (open-label)</td>
<td>515</td>
<td>0.19 (0.01-1.08)</td>
</tr>
</tbody>
</table>

Median Follow-up in Open-Label Phase 18.4 months (17.5-19.1)

97% relative reduction vs. placebo
### The PROUD Trial

**Multi-center Open-label randomized trial in GUM clinics**

- **Immediate Daily Oral TDT/FTC**
  - (n = 275)

- **Deferred Daily TDF/FTC by 12 months**
  - (n = 269)

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**HIV-negative Gay Men and transgender women reporting unprotected anal intercourse with a man within last 90 days**

- **Primary endpoint**: Time to accrual of 500 participants and retention
- **From June 2014**: HIV-infection in first 12 months
- **Other outcome measures**: safety, adherence, risk compensation
- All participants will be offered a risk reduction package: regular HIV testing, diagnosis and treatment of STIs, support to reduce high risk behavior including condoms, PEP.
- Visits every 3 months with HIV testing using ELISA or rapid tests

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S. Mc Cormack et al Lancet 2016
# Efficacy of Daily PrEP in MSM in the UK

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of infections</th>
<th>Follow-up (PY)</th>
<th>Incidence (per 100 PY)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>23</td>
<td>465</td>
<td>5.0</td>
<td>3.5–6.9</td>
</tr>
<tr>
<td>Immediate</td>
<td>3</td>
<td>243</td>
<td>1.2</td>
<td>0.4–2.9</td>
</tr>
<tr>
<td>Deferred</td>
<td>20</td>
<td>222</td>
<td>9.0</td>
<td>6.1–12.8</td>
</tr>
</tbody>
</table>

**Efficacy** = **86%** (90% CI: 64–96%)

**P-value** = 0.0001

**Number Needed to Treat** = **13** (90% CI: 9 – 23)

S. McCormack et al Lancet 2016
INFECTIONOUS DISEASES

Doubts dispelled about HIV prevention

New studies show remarkable efficacy and versatility of drugs for uninfected

By Jon Cohen, in Seattle, Washington

It was great news for HIV prevention, and few seemed to hear it. Five years ago, researchers showed that people likely to be exposed to HIV can cut their risk of infection with a simple pill, but the strategy has been slow to catch on.

At the Conference on Retroviruses and Opportunistic Infections (CROI) here last week, a bevy of new studies quelled most remaining doubts about the real-world effectiveness of what’s known [is] the Achilles’ heel of PrEP,” said Jean-Michel Molina of Paris Diderot University.

In a study called IPERGAY, Molina and his colleagues investigated whether PrEP might work better if people did not have to take pills every day. They tested a more convenient “on-demand” regimen in 414 HIV-negative, high-risk MSM in France and Canada. The men were instructed to take pills—without knowing whether they contained Truvada or a placebo—before and after having sex. As Molina ex-

545 MSM in the Uni conventional regime participants and cc lor and HIV infectio group that started I design differed from MSM in two key w a placebo, and part used, the pills offer PROUD was stopi ple in the deferred g compared with thre treated gr

Science March 16, 2015
Oral PrEP should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches.

Defining “substantial risk”: Substantial risk of HIV infection is provisionally defined as HIV incidence greater than 3 per 100 person–years in the absence of PrEP. HIV incidence greater than 3 per 100 person–years has been identified among some groups of men who have sex with men, transgender women in many settings and heterosexual men and women who have sexual partners with undiagnosed or untreated HIV infection.
• PrEP recommended in HIV-negative MSM and transgender individuals when condoms are not used consistently with casual partners or with HIV-positive partners who are not on treatment.

• A recent STD, use of PEP or chemsex may be markers of increased risk for HIV acquisition.

• PrEP provides a high level of protection against HIV acquisition but does not protect against other STDs: to be used in combination with other preventive interventions.

• Document a negative 4th generation HIV test prior to starting PrEP. This test should be repeated every 3 months.

• TDF/FTC 300/200 mg 1 tablet qd or On Demand for MSM (2 pills 2-24h before sex followed by two single doses, 24 and 48 hours after the first drug intake).
EACS e-Learning

PrEP online course newly added

www.eacssociety.org

PrEP: Pre-Exposure Prophylaxis Online Course

Applications are now open!

Application form

Fill in the application form and send it to Ms. Anne Grevsen at HIVonlinecourse@eacssociety.org

Contact

Ms. Anne Grevsen
HIVonlinecourse@eacssociety.org
3700 recruited from 03/01/2016 to 10/31/2016 and dispensed PrEP at baseline

- 62 No HIV follow-up test (1.7%)
- 49 Withdrawal from study
  - 20 no longer at risk of HIV infection
  - 8 side effects
  - 4 moved out of jurisdiction
  - 6 can no longer attend
  - 2 tired of taking pills every day
  - 3 eGFR dropped below 60 ml/mn
  - 6 others
- 3069 (83%) with visit M12 or later

EPIC Study in MSM in NSW

- 2 new HIV infections:
  - 1 was dispensed but never commenced PrEP
  - 1 took no PrEP for months prior to infection

HIV Incidence rate: 0.048/100 person-years (95%CI 0.012-0.195)

4,100 PY by 10/31/2017 for HIV incidence

Grulich A. et al. Lancet HIV 2018
# Adverse Events

<table>
<thead>
<tr>
<th>Nb Participants (%)</th>
<th>TDF/FTC n=199</th>
<th>Placebo n=201</th>
<th>TDF/FTC n=362</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AEs</td>
<td>186 (93)</td>
<td>181 (90)</td>
<td>353 (98)</td>
</tr>
<tr>
<td>Severe AEs</td>
<td>20 (10)</td>
<td>17 (8)</td>
<td>40 (11)</td>
</tr>
<tr>
<td>Grade 3 or 4 AEs</td>
<td>19 (10)</td>
<td>15 (7)</td>
<td>40 (10)</td>
</tr>
<tr>
<td>AEs leading to Rx D/C</td>
<td>1</td>
<td>0</td>
<td>3*</td>
</tr>
<tr>
<td>GI-related AEs</td>
<td>28 (14)</td>
<td>10 (5)</td>
<td>48 (13)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>16</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8</td>
<td>6</td>
<td>25</td>
</tr>
</tbody>
</table>

**Decrease in plasma creatinine clearance to 48, 71 and 76 ml/mn

Molina et al Lancet HIV 2017
**eGFR: TDF/FTC vs Placebo**

Mean slope of eGFR decline per year

**TDF/FTC**: \(-1.88 \text{ mL/min/1.73m}^2\)

**Placebo**: \(-1.53 \text{ mL/min/1.73m}^2\)

\[ P=0.27 \]
Selection of Drug Resistance in Clinical Trials with TDF/FTC for PrEP

- Resistance rare in clinical trials of PrEP
- RAMs assessed: K65R (TDF, FTC), K70E (TDF) or M184V/I (FTC)
- Resistance when seroconverting in the TDF/FTC arm: M184V/I (1 K65R)

<table>
<thead>
<tr>
<th>Trial</th>
<th>N (TDF/FTC)</th>
<th>Seroconverted after enrollment Nb resistance / total</th>
<th>Acute Infection At enrollment Nb resistance / total</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx</td>
<td>1224</td>
<td>0/48</td>
<td>2/2</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>1579</td>
<td>0/21</td>
<td>2/4</td>
</tr>
<tr>
<td>TDF2</td>
<td>611</td>
<td>0/9</td>
<td>1/1</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>1062</td>
<td>4/33</td>
<td>0/1</td>
</tr>
<tr>
<td>VOICE</td>
<td>1003</td>
<td>1/61</td>
<td>2/9</td>
</tr>
<tr>
<td>PROUD</td>
<td>275</td>
<td>0/2</td>
<td>2/3</td>
</tr>
<tr>
<td>IPERGAY</td>
<td>199</td>
<td>0/2</td>
<td>0/2</td>
</tr>
<tr>
<td>TOTAL</td>
<td>5953</td>
<td>5/176 (&lt; 3%)</td>
<td>9/22 (41%)</td>
</tr>
</tbody>
</table>

Adapted from Parikh and Mellors, Curr Opin HIV AIDS 2016
PrEP in France Today

- PrEP with TDF/FTC approved and free since 01/16
- Adults at high risk of sexual acquisition of HIV
- Generic TDF/FTC available since July 2017
- Condoms also reimbursed since December 2018
PrEP Delivery is Integrated into Existing Services in France

- Hospitals HIV clinics (01/2016)
- STI clinics (06/2016)
- GP can renew prescriptions (02/2017)
- Antiretrovirals delivered in hospital or private pharmacies
Est. numbers on PrEP:

- <100
- 100 - 1,000
- 1,000 – 10,000
- 10,000 – 100,000
- >100,000

Data from AVAC.org
https://www.prepwatch.org/country-updates/
New HIV Diagnoses and Nb of PrEP Users

- **United States**
  - HIV incidence: 40,000
  - PrEP Users: 200,000
  - Ratio: 5:1

- **France**
  - HIV incidence: 6,000
  - PrEP Users: 12,000
  - Ratio: 2:1

- **Australia**
  - HIV incidence: 1,100
  - PrEP Users: 14,600
  - Ratio: 13:1

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Decline in HIV-Infections among MSM in the Epic Study (NSW)

Grulich A. et al et al Lancet HIV 2018

25% decline 2015-2017

PrEP
Status of PrEP Implementation in Europe (November 2018)

Nationally available (reimbursed)
Ongoing pilot or research project
Generics available in healthcare settings (not reimbursed)
Not formally implemented

Source: ECDC. Dublin Declaration monitoring 2018; validated unpublished data.
How to Upscale PrEP Implementation?

• Increase awareness about this new preventive tool

• Integrate PrEP with other health care services
  – Increase No. sites to deliver PrEP: training, task shifting, rapid appointments, rapid PrEP start
  – Involve GPs

• Extend PrEP beyond MSM to other high risk groups
National Prevention Campaign for MSM
MAIRIE DE PARIS

VERS PARIS SANS SIDA
est une association loi de 1901

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est une association loi de 1901

FAISONS
DE PARIS LA VILLE DE
L’AMOUR
SANS SIDA

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OU DANS L’UN DES 11 CENTRES
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AIDES Advertising Campaign 2018

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VOS PROTÈGE DU VIH

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Pour savoir comment en bénéficier : aides.org/prep

AIDES

PrEP

le désir
PrEP in the Future

✓ Ideally: high efficacy, safety and tolerability, convenience, low cost
✓ Multiple choices to accommodate everyone
✓ Combination of drugs and/or contraceptives
Aids and HIV

Truvada and the truth: is HIV prevention propelling the STI epidemic?

Benjamin Ryan
Sun 21 Oct 2018 07.00 EDT
STIs in PROUD

Caveat
Number of screens differed between the groups:
e.g. Rectal gonorrhoea/chlamydia
974 in the IMM group and 749 in the DEF

Mc Cormack et al Lancet 2016
New Diagnoses of STIs from 1996 to 2015 in MSM in England

Unemo M et al. Lancet Infect Dis 2017
Historic Trends in Gonorrhea in the UK

Dramatic Increases in Bacterial STI Incidence in Era of Effective HIV Treatment and Prevention

WHO 2016 Estimates: adults 15 to 49
376 million new cases of curable STI
Curable STI (Chlamydia, gonorrhoea, syphilis and trichomoniasis)

The STATE of STDs in the United States

- 1.59 million CASES OF CHLAMYDIA 4.7% increase since 2015
- 468,514 CASES OF Gonorrhea 18.5% increase since 2015
- 27,814 CASES OF Syphilis 17.6% increase since 2015

STDS TIGHTEN THEIR GRIP ON THE NATION’S HEALTH AS RATES INCREASE FOR A THIRD YEAR

- Gonorrhea: continued antimicrobial resistance
- Syphilis: incidence above pre-AIDS era in MSM, spread into heterosexual networks
- Reappearance of classics: LGV proctitis

https://www.cdc.gov/std; Pathela Sex Transm Dis 2019; WHO; Oliver Clin Infect Dis 2018; Braun DL Clin Infect Dis 2018

Marrazzo JM. Plenary session. CROI 2019 Seattle USA March 2019
Meta-Analysis of Effect of PrEP on STIs Diagnosis among MSM

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant et al 2014</td>
<td>1.35 (.83–2.19)</td>
<td>12.10</td>
</tr>
<tr>
<td>Corales et al 2015</td>
<td>0.41 (.07–1.87)</td>
<td>1.66</td>
</tr>
<tr>
<td>Liu et al 2016</td>
<td>0.96 (.71–1.29)</td>
<td>18.91</td>
</tr>
<tr>
<td>McCormack et al 2016</td>
<td>1.07 (.78–1.46)</td>
<td>18.32</td>
</tr>
<tr>
<td>Gulob et al 2016</td>
<td>1.39 (.76–2.55)</td>
<td>9.10</td>
</tr>
<tr>
<td>Marcus et al 2016</td>
<td>1.48 (1.18–1.85)</td>
<td>22.32</td>
</tr>
<tr>
<td>Montano et al 2017</td>
<td>0.98 (.58–1.65)</td>
<td>11.06</td>
</tr>
<tr>
<td>Lal et al 2017</td>
<td>2.99 (1.42–6.51)</td>
<td>6.53</td>
</tr>
<tr>
<td>Overall</td>
<td>1.24 (.99–1.54)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

- Significant increase in any **rectal STI** diagnosis (OR: 1.39, 95% CI: 1.03-1.87)
- Significant increase in **rectal chlamydia** (OR: 1.59, 95% CI: 1.19-2.13)
- Increase in STIs rates in more **recent studies** (OR: 1.47, 95% CI: 1.05-2.05)

Traeger MW et al. CID 2018
How to Contain the STIs Epidemic?

- A, B and C: promotion of condom use
  - Counseling and behavioral interventions

- Vaccines
  - Viral STIs (hepatitis A and B, HPV)
  - Bacterial STIs (gonorrhea, chlamydia, syphilis)

- Test and Treat
  - Regular testing for STIs in high risk individuals
  - Early treatment might reduce long term incidence

- Partner notification and treatment

- Antibiotic Prophylaxis
Sulfathiazole was very effective: not a single case of chancroid in 450 men and a single case of GC which proved to be refractory to treatment with sulfonamides!
Neisseria gonorrhoeae

- NG has an extraordinary capacity to alter its genetic material
- It is naturally competent for transformation and can also change its genome through all types of mutations
Randomized Open-Label Trial (July 2015 - July 2016)

- HIV-negative high risk MSM
- Enrolled in the ANRS IPERGAY Open-label extension study
- No contra-indication to Doxy

On Demand PEP with Doxycycline
(200 mg ~ 24h after sex, up to 72h)*
No PEP

- No more than 6 pills/week to limit AB exposure and selection pressure
- With 276 subjects enrolled: 80% power to detect a 55% relative decrease in incidence of a first STIs with PEP (expected incidence: 40/100 PY with no PEP)
- Visits: 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

Molina et al Lancet ID 2018
**Why Testing Doxycycline PEP?**

- Doxycycline successful for prevention of Lyme disease and Leptospirosis (Nadelman, NEJM 2001; Takafuji, NEJM 1984)
- Randomized study in 30 HIV+ MSM with prior syphilis: fewer STIs (6 vs. 15) with daily doxycycline (Bolan, Sex Trans Infect 2015)
- Limited use of doxycycline in France for the treatment of bacterial infections, mostly used for acne and malaria prophylaxis
- No known resistance to doxycycline in *C. trachomatis* and *T. pallidum* and > 50-75% of *N. gonorrhoeae* in France already resistant
- IPERGAY: unique opportunity to test an intervention directed at STIs:
  - Participants at high risk of STIs with monitoring every 2 months
  - No access to PrEP outside the study: high retention expected
  - Participants thankful to the study team and ready to test a new intervention
Chlamydiae: a distinct phylogenetic lineage among Gram-negative bacteria and very limited evidence of horizontally acquired foreign DNA

No tetracyclines identified so far in humans (O’Neil et al. Microbiology 2013) and rare macrolide resistance (4 strains)

Phenotypic or “heterotypic resistance” at high infectious loads: subpopulation of persister cells with reduced growth rate, less susceptible to antimicrobials

C. suis: tetracycline resistance in pigs with a tetC gene encoding an efflux pump and horizontal transfer in vitro to C. trachomatis (Dugan et al. Antimicrob Agents Chemother 2004) and horizontal transfer in vivo encoding tetracyclins (Sandoz and Rockey Future Microbiol 2010; 5:1427)
Treponema pallidum

- Complete genome sequence: lack of genetic elements (plasmids, bacteriophage, transposons) associated with horizontal gene transfer mechanisms (Fraser et al, Science 1998)

- Lack of penicillin resistance after more than 6 decades

- Multistep mutational process may be required for penicillin resistance (3 putative PBPs)

- Macrolide-resistant strains have emerged in 1977 now prevalent in several developed countries: single point mutation in both 23S rRNA genes

- Tetracycline resistance is a concern since single point mutations in the 16S rRNA gene could select for resistance as reported in other bacteria

- Doxycycline is currently recommended for the treatment of syphilis in patients with penicillin allergy

Stamm et al. Antimicrob Ag Chem 2010; 54:583
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PEP Doxy (n = 116)</th>
<th>No PEP (n = 116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>38 (33-48)</td>
<td>39 (32-44)</td>
</tr>
<tr>
<td>White</td>
<td>110 (95)</td>
<td>110 (95)</td>
</tr>
<tr>
<td>Completed secondary education</td>
<td>109 (94)</td>
<td>103 (89)</td>
</tr>
<tr>
<td>Single</td>
<td>82 (71)</td>
<td>81 (70)</td>
</tr>
<tr>
<td>Use of psychoactive drugs*</td>
<td>49 (42)</td>
<td>49 (42)</td>
</tr>
<tr>
<td>Circumcised</td>
<td>28 (24)</td>
<td>21 (18)</td>
</tr>
<tr>
<td>Infection with NG, CT or TP **</td>
<td>22 (19)</td>
<td>16 (14)</td>
</tr>
<tr>
<td>Nb sexual acts in prior 4 weeks</td>
<td>10 (5-15)</td>
<td>10 (5-20)</td>
</tr>
<tr>
<td>Nb sexual partners in prior 2 months</td>
<td>10 (5-15)</td>
<td>10 (4-20)</td>
</tr>
</tbody>
</table>

* in last 12 months: ecstasy, crack, cocaine, crystal, speed, GHB/GBL
** NG: Neisseria gonorrhoeae, CT: Chlamydia trachomatis, TP: Treponema pallidum
Median follow-up of 8.7 months (IQR: 7.8-9.7): 73 subjects infected

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

Hazard Ratio: 0.53 (95% CI: 0.33-0.85, p=0.008)

71% of STIs were asymptomatic
Incidence of Gonorrhea (ITT Population)

Median follow-up of 8.7 months (IQR: 7.8-9.7): 47 subjects infected

25 in no PEP arm (incidence: 34.5/100 PY), 22 in PEP arm (incidence: 28.7/100 PY)

Hazard Ratio: 0.83 (95% CI: 0.47-1.47, p=0.52)
# Sites of Gonorrheal 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>Total sites</td>
<td>27</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total infections</th>
<th>PEP Doxy</th>
<th>No PEP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections per 100 py</td>
<td>27</td>
<td>30</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>32.6</td>
<td>37.3</td>
<td></td>
</tr>
</tbody>
</table>

Molina et al Lancet ID 2018
Incidence of Chlamydia (ITT Population)

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 Syphilis (ITT Population)

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)
**AB Resistance**

- **N. gonorrhoeae**: 70 infections by PCR in 56 participants including BL
  - Culture attempted in 28 pts (40%)
    - 9/28 samples (32%): positive culture in 8 pts (2 PEP, 6 no PEP) and high level tetracycline resistance in 4 patients, all with no PEP
  - Genotypic resistance (tetM, S10 protein): 70 samples from 43 pts
    - 31/38 (81.5%) pts with resistance, 6/38 (15.8%) at high level
    - No difference between arms (p=0.4)

- **C. trachomatis**
  - Chlamydia isolation attempted in 22 anal and 2 oral swabs
  - Successfull in 5 (21%) strains from 4 pts, all susceptible to doxycycline
Summary of Doxycycline PEP

- Doxycycline PEP reduced the overall incidence of bacterial STIs by 47% in MSM on PrEP (8.7 months of FU)
- No effect on Gonorrhea but strong reduction (70-73%) in Chlamydia and Syphilis incidence
- Acceptable safety profile with mild/moderate GI AEs
- Analysis of antibiotic resistance very limited
- Impact on human microbiome not assessed
- Long-term benefit of PEP remains largely unknown

Antibiotic prophylaxis for STIs **NOT recommended**

Additional studies to be conducted to assess benefit/risk ratio

Molina et al Lancet Inf Dis 2018
What is Next?

- **Canada**: Pilot studies with daily doxycycline in MSM to prevent syphilis

- **Australia**: Syphylaxis study: impact of daily doxycycline on the incidence of syphilis in PrEP users in Sydney

- **USA**
  - Spinelli et al. STI 2019: Grindr survey in SF in 1300 MSM High acceptability of PEP for STIs: 84%
  - DoxyPEP study among MSM on PrEP on living with HIV

- **France**
  - New Doxy PEP study in the ANRS Prevenir PrEP study in MSM with the evaluation of the Meningococcal B vaccine against gonorrhea
Summary

• High incidence of HIV infection in high risk groups
• PrEP highly effective preventive tool and people at risk should have access
• PrEP/condoms + testing + treatment of HIV-infection should be scaled-up to contain the HIV epidemic
• Reduced condom use and high STIs rates did not undermine PrEP efficacy
• STIs have become a new priority in PrEP users and more research is needed to improve prevention, treatment and partner notification
• 2030 WHO/UNAIDS target: reduce incidence of HIV and STIs by 90%
Acknowledgments