HIGH PREVALENCE AND ANTIBIOTIC RESISTANCE OF *M. GENITALIUM* INFECTIONS IN MSM ON PREP

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Background

Mycoplasma genitalium (MG) is an emerging pathogen among MSM evolving into so called superbugs with raising rates of antibiotic resistance. The emergence of **antimicrobial resistance** (AMR) in this bacterium has reduced treatment options. Recommended treatment for uncomplicated MG infections is azithromycin (AZM) 500 mg followed by then 250 mg 2-5 days or moxifloxacin (MXF) 400 mg od 7-10 days (1).

In 2017, clinical acquired resistance of MG to macrolides were in elevation in Europe (10-61%), in Australia (40-68%) and in US (48%-58%). Emergence of clinical acquired resistance to fluoroquinolones (FQ) ranged from 4.5% (UK) to 47% (Japan) (2-3).

AZM and FQ resistance are mainly due to mutations in the macrolide target (23S rRNA) or mutations in the FQ target (topoisomerase IV), respectively. Tetracyclines have low eradication rate for MG clinically but no acquired resistance was described.

Objectives

The aims of this study were

1) to assess the prevalence and incidence of MG infection in MSM enrolled in the open-label phase of the ANRS IPERGAY trial (4) with on demand TDF/FTC for HIV prevention
2) to study the impact of doxycycline post-exposure prophylaxis (**DOXY PEP**) on incidence of MG infection.

Patients & Methods

During the open-label phase of the ANRS IPERGAY trial, participants were enrolled in a prospective randomized (1:1) open-label sub-study of post-exposure prophylaxis (PEP) with doxycycline (5). All subjects were tested at baseline and 6 months by **real-time PCR assays** for MG detection in urine samples and the results were given to clinicians. By contrast, the 2 others sites (oro-pharyngeal and anal) were screened retrospectively at the end of the study **from frozen samples**.

Detection of MG was performed by using *C. trachomatis/Ureaplasma/M. genitalium* Real-TM kit (Sacace, Biotechnologies) on urines or the Cobas 6800 assay (Roche diagnostics) on anal and throat swab samples.

Resistance to AZM and to FQ were investigated **retrospectively** on PCR positive tubes by the detection of mutations in 23S rRNA gene (ResistancePlusTM MG test, SpeeDx, Australia) and in *parC* gene (PCR and sequencing), respectively.

Statistics

Differences in percentages were tested using Chi-square test or Fisher exact test as appropriate. All P values and confidence intervals are two-sided. Analyses were conducted using SAS software (version 9.3, SAS Institute).

Results

Prevalence and Incidence of *M. genitalium* in MSM on PrEP

- **Prevalence at baseline:**

From July 2015 to January 2016, 210/232 (90.5%) participants randomized in the PEP study were tested.
Prevalence of MG at baseline was 10.5% all sites combined (Table 1).
All patients had only one site positive for MG. Only one patient was symptomatic (burning at urination).

Patients with PCR +	Prevalence of MG (%) 95% Confidence Interval	DOXY PEP	No PEP
First void urine	**6.3%** [3.4% - 10.8%]	6/103 (6%)	7/102 (7%)
Anus	**4.3%** [1.9% - 8.6%]	3/93 (3%)	5/91 (5%)
Throat	**0.5%** [0.01% - 2.8%]	0/99 (0%)	1/98 (1%)
TOTAL	**10.5%** [6.6% - 15.9%]	9/107 (8%)	13/103 (13%)

Table 1. Prevalence of MG infection at baseline in MSM on PrEP **at entry in the DOXY PEP substudy**

- **New infections at 6 months:**

Eleven participants had acquired a MG infection at the 6-month visit, 7 participants in the PEP arm and 4 in the no PEP arm. These infections were detected in urine (n=5), anus (n=6) or throat (n=1, combined with anus*) (Table 2). All patients were asymptomatic.

Patients with PCR +	New MG infection (%) 95% Confidence Interval	DOXY PEP	No PEP	P value
First void urine	**3.1%** [1% - 7.3%]	2/81 (2.4%)	3/79 (3.8%)	0.68
Anus	**3.7%** [1.4% - 8.1%]	5/84 (5.9%)	1/78 (1.2%)	0.21
Throat	**0.6%** [0.01% - 3.2%]	1/89 (1.1%)	0/84 (0%)	1.00

Table 2. New MG infections at 6 months in MSM on PrEP with or without post- prophylaxis with doxycycline.

The incidence of MG infections did not differ by arm (doxycycline PEP or no PEP).

Resistance of *M. genitalium* in MSM on PrEP

- **Resistance**

39 samples obtained from 30 patients were available for the detection of resistance to AZM and MXF.
- 28 from the prevalent infections (21 prevalent infections tested at D0 and among them 7 re-tested at M6 for persistent infections)
- 11 from the new infections at M6

The overall rate of MG resistance to **AZM and FQ was 69.6%** (16/23; 7 not amplifiable; 95%CI=[47%-87%]) **and 14.8%** (4/27; 3 not amplifiable; 95%CI=[4%-34%]), respectively.
Antibiotic resistance of MG isolates were explained by substitution of A2058G/T (n=7) or A2059G (n=9) in the 23S rRNA for AZM and by substitutions S83I, S83B, D87Y and A88T in the QRDR of the topoisomerase ParC for MXF.

- **Outcome of MG URINARY infections**

Treatment response of urinary MG infection was investigated according to resistance at diagnosis.
For urinary MG infections treated by AZM, 11/18 were retrospectively tested for macrolides resistance and had a test of cure with PCR assay after treatment. According to the PCR results, 7 infections were cured and 4 were not. All (5/5) MG infections with a wild type isolate were cured whereas only 2/6 infections with mutations in 23S rRNA were cured (Table 3).

Macrolides mutation at diagnosis	Cured	Persistence	P value
Wild Type	5	0	0.06
Mutation in 23S rRNA	2	4	
TOTAL	7	4	

Table 3. Treatment response of urinary *M genitalium* infection according to MACROLIDES **resistance at diagnosis**

Conclusions

- In this study, a high prevalence of MG infection among MSM on PrEP with on demand TDF/FTC was observed (10.5%), with infection mainly observed in urine or anus, as previously reported (6). The majority of cases were asymptomatic.
- MG isolates found in MSM on PrEP were highly resistant to AZM (69.6%) and to MFX (14.8%).
- Post-exposure prophylaxis with doxycycline had no impact on the incidence on MG infections in our study.
- Our results are in agreement to the new French recommendations to avoid screening of asymptomatic individuals for MG, and avoid treatment of asymptomatic MG infection, in order to avoid untreatable MG strains.

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