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**Prévalence élevée d'infection à *Mycoplasma genitalium* et de résistance aux macrolides  
chez les usagers de la prophylaxie pré-exposition contre l'infection VIH**

**High prevalence of *Mycoplasma genitalium* infection and macrolide resistance in patients  
enrolled in HIV pre-exposure prophylaxis program**

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**Mots clés :** prophylaxie pré-exposition ; *Mycoplasma genitalium* ; macrolides

**Keywords:** pre-exposure prophylaxis; *Mycoplasma genitalium*; macrolides

## Résumé

**Objectifs.** Déterminer la prévalence et la résistance aux macrolides des infections à *M. genitalium* chez les usagers de PrEP.

**Patients et méthodes.** Recherche systématique et prospective des infections à *M. genitalium* à la consultation PrEP du CHU de Bordeaux (inclusion entre janvier 2016 et février 2017).

**Résultats.** Sur 89 personnes, nous rapportons une prévalence des infections à *M. genitalium* de 10 % (majoritairement asymptomatiques), aussi élevée que celle des autres IST classiquement testées, avec un taux élevé (58 %) de résistance aux macrolides.

**Conclusions.** Compte tenu du fort taux de résistance aux macrolides, une recherche systématique de la résistance aux macrolides dans les infections à *M. genitalium* peut être recommandée avant d'envisager une antibiothérapie.

## Summary

**Objectives.** Limited data on *Mycoplasma genitalium* infection has been reported among PrEP users. The aim of this study was to estimate the prevalence and macrolide resistance of *M. genitalium* infection among enrollees in a French PrEP program.

**Patients and methods.** *M. genitalium* infection screening was systematically and prospectively proposed to patients of the Bordeaux PrEP program (between January 2016 and February 2017). Macrolide resistance was evaluated in *M. genitalium*-positive patients.

**Results.** Among 89 clients, *M. genitalium* infection prevalence was 10% (mainly asymptomatic) with a high rate of macrolide resistance (58%).

**Conclusions.** Because of a high level of macrolide resistance, a systematic search for *M. genitalium* macrolide resistance associated-mutations may be recommended in PrEP users before initiating the antibiotic therapy.

## Introduction

*Mycoplasma genitalium* is a recognized and emerging sexually transmitted pathogen [1]. A meta-analysis reported a strong association between *M. genitalium* and HIV infection, especially in African populations [2]. A cohort study reported a positive relation between *M. genitalium* infection and the risk of HIV-1 acquisition in African women [3]. Moreover, in a British study of 438 men who had sex with men (MSM), *M. genitalium* infection was significantly associated with HIV positivity (OR 7.6, 95% CI 3.2 to 18.7,  $p < 0.001$ ), in contrast to other sexually-transmitted infections (STIs) such as *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections [4].

HIV pre-exposure prophylaxis (PrEP) is predominantly proposed to MSM, in whom many STIs are diagnosed [5, 6]. No reliable data has been reported on *M. genitalium* infection in such populations in France because the screening of this bacterium is usually not routinely performed. Macrolide antibiotics are the first-line treatment for *M. genitalium* infections. In the Bordeaux University Hospital, southwestern France, before the PrEP introduction, the prevalence of macrolide resistance-associated mutations among *M. genitalium*-positive patients ranged between 8.3% [7] and 17.2% [8]. Macrolide resistance rates up to 40% have been reported in several countries [9].

The aim of this study was to estimate the prevalence of *M. genitalium* infection among enrollees in a PrEP program. Macrolide resistance was evaluated in *M. genitalium*-positive patients.

## Material and methods

The patients of the Bordeaux PrEP program were included between January 2016 and February 2017, with follow-up until June 2017. Detection of *M. genitalium* was performed

using the Aptima® *M. genitalium* assay (Hologic, USA) at program entry, and then every six months. The search for macrolide resistance-associated mutations in the 23S rRNA encoding gene was performed using real-time PCR [10]. Urogenital and anal specimens were prospectively collected. The study was performed with oral informed consent in accordance with French ethical guidelines (CNIL agreement #2043908).

## Results

A total of 88 MSM and one male to female transgender were registered in the PrEP clinic. Their median age was 34.9 years (interquartile range [IQR], 28.1-44.1). The median follow-up was 6.9 months (IQR, 5.3-9.2). Sixty-three out of 87 respondents (72.4%) reported at least one previous episode of STI. PrEP was prescribed to 77 (86.5%) of those registered and 69 came back at least once for a follow-up clinic visit. Regarding STI screening, *N. gonorrhoeae* was the most prevalent and incident bacterium (mainly asymptomatic cases) (Table 1). A total of 26 *M. genitalium*-positive samples were collected from 18 MSM, nine at baseline and nine during follow-up. The anorectum was the most commonly infected site (15/26, 57.7%), followed by the urethra (9/26, 34.6%), and the oropharynx (2/26, 7.7%). Prevalence and incidence of *M. genitalium* and other STIs were high (Table 1). *M. genitalium* prevalence was 10.1% (9/89) (95% confidence interval [CI], 4.7-18.3) at baseline, and the incidence was 17.4/100 person-years (PY) (95% CI, 9.1-33.5) (Table 1). *M. genitalium* prevalence and incidence per anatomical site were 5.6% (1.8-12.6) and 11/100 PY (5.0-14.5) in anus, 3.4% (0.7-9.5) and 3.6/100 PY (0.9-14.5) in first-void urine, and 1.1% (0.03-6.1) and 1.8/100 PY (0.2-12.5) in oropharynx. The 18 *M. genitalium*-infected patients were predominantly asymptomatic with only two patients presenting with a symptomatic but moderate urethral

discharge. Notably, the 11 patients with at least one anal *M. genitalium*-positive sample were all asymptomatic.

The samples from nine *M. genitalium*-positive individuals showed resistance to macrolides, two of which were acquired resistance after first-line macrolide treatment (extended azithromycin regimen in both cases). Five patients' samples presented a wild-type phenotype, and samples from the remaining four patients were not amplified by real-time PCR targeting 23S rRNA because of low *M. genitalium* DNA load. Overall, excluding patients with non-amplified samples (n=4) and patients with acquired resistance during treatment (n=2), macrolide resistance was detected at baseline in 58% (7/12) of patients.

## **Discussion**

We reported the first results of a study conducted in a urban PrEP clinic of southwestern France. *M. genitalium* infection was frequent (prevalence of 10.1%) among male attendees. This prevalence was higher than that we had reported in 2016 in a more general population attending our university hospital (3.4%, 95% CI 2.8-4.2) [11].

Prevalence of macrolide resistance in this specific population was also higher than expected. We previously collected 369 *M. genitalium*-positive urogenital specimens in 2013-2014 in the same hospital and the macrolide resistance rate was 17.20% (38/221; 95% CI 12.79%-22.72%), comparable in both years [8]. In 2016, we reported a prevalence of macrolide resistance in male and female clinical samples of 8.3% (6/72) [7]. However, in an STI clinic in Australia, the frequency of macrolide resistance reached 100% in *M. genitalium*-positive rectal specimens from male patients [12].

Azithromycin, especially the single dosage of 1 g, is associated with the development of macrolide resistance in *M. genitalium*, and is likely to increase the circulation of macrolide-



resistant strains in the population. Consequently, single-dose azithromycin is no longer recommended in Europe as first-line treatment for non-gonococcal urethritis [13]. The recommended treatment for uncomplicated macrolide-resistant *M. genitalium* infection is moxifloxacin 400 mg once daily for 7–10 days [9]. In this context, prevention measures and condom use should be enhanced.

The asymptomatic anorectal *M. genitalium* infection was the most frequent presentation. We also previously reported a high frequency (71%) of asymptomatic carriage of *M. genitalium* [11]. Among Australian MSM, rectal infection was more commonly reported than urethral infections: 42% and 8%, respectively [14]. Two cases of asymptomatic oropharyngeal infection were also reported in the present study, which is not usually reported in the literature.

Because a positive relation between *M. genitalium* infection and the risk of HIV-1 acquisition has been highlighted in previous studies, and because PrEP users may be a possible silent reservoir for *M. genitalium* transmission, a systematic screening for *M. genitalium* including at least one anal sample appears of public health interest in PrEP programs. Furthermore, the high rate of macrolide resistance in this specific population implies a systematic search for macrolide resistance-associated mutations, as per European recommendations [9]. Molecular technologies present the advantage of treatment guidance.

Macrolide resistance in rectal samples from MSM is also of clinical concern with emerging difficult-to-treat cases. Further studies are required to determine the best antibiotic management of *M. genitalium* infections in PrEP programs.

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**Table 1.** Sexually-transmitted infections diagnosed during the regular screening of 89 HIV PrEP users in Bordeaux University Hospital, Southwestern France.

**Tableau 1.** Infections sexuellement transmissibles diagnostiquées chez 89 personnes suivies dans le programme PrEP du CHU de Bordeaux.

|                                 | <b>Cases diagnosed at inclusion</b> | <b>Prevalence % [95% CI]</b> | <b>Cases diagnosed during follow-up</b> | <b>Incidence† % [95% CI]</b> |
|---------------------------------|-------------------------------------|------------------------------|---|------------------------------|
| <i>N. gonorrhoeae</i> *         | 11                                  | 12.4 [6.3 ; 21.0]            | 10                                      | 19.3 [10.4 ; 35.9]           |
| <i>C. trachomatis</i> *         | 11                                  | 12.4 [6.3 ; 21.0]            | 8                                       | 15.3 [7.7 ; 30.7]            |
| <i>M. genitalium</i> *          | 9                                   | 10.1 [4.7 ; 18.3]            | 9                                       | 17.4 [9.1 ; 33.5]            |
| <b>Syphilis</b>                 | 4                                   | 4.5 [1.2 ; 11.1]             | 2                                       | 3.6 [0.9 ; 14.3]             |
| <b>Indeterminate urethritis</b> | 0                                   | 0                            | 5                                       | 9.1 [3.8 ; 21.8]             |

PrEP: HIV pre-exposure prophylaxis; 95 % CI: 95% confidence interval.

\* Detected in throat, first-void urine, or rectum

† Incidence per 100 person-years