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Short communication

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

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

M. Deborde[a], S. Pereyre[b,c,d], M. Puges[a], C. Bébéar[b,c,d], A. Desclaux[a], M. Hessamfar[e,f,g], C. Le Roy[b,c], F. Le Marec[e], F. Dabis[e,f], C. Cazanave[a,b,c,*]

[a] *Infectious and tropical diseases department, Pellegrin hospital, Bordeaux university hospital, 33000 Bordeaux, France*
[b] *USC EA 3671, Mycoplasma and chlamydia human infections, Bordeaux university, 33000 Bordeaux, France*
[c] *USC EA 3671, Mycoplasma and chlamydia human infections, French National Institute for Agricultural Research, 33000 Bordeaux, France*
[d] *Bacteriological laboratory, Bordeaux university hospital, 33000 Bordeaux, France*
[e] *Inserm U1219 – Bordeaux population health, institute for public health, epidemiology, and development (ISPED), Bordeaux university, 33000 Bordeaux, France*
[f] *COREVIH Aquitaine, Bordeaux university hospital, 33000 Bordeaux, France*
[g] *Infectious diseases and internal medicine department, Saint-André hospital, Bordeaux university hospital, 33000 Bordeaux, France*

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Abstract

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.

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.

Mots clés : Prophylaxie pré-exposition ; *Mycoplasma genitalium* ; Macrolides

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* Corresponding author. Service des maladies infectieuses et tropicales, hôpital Pellegrin, place Amélie Raba-Léon, 33076 Bordeaux cedex, France.
E-mail address: charles.cazanave@chu-bordeaux.fr (C. Cazanave).

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1. 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.

2. 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).

3. 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.

4. 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

Table 1
Sexually-transmitted infections diagnosed during the regular screening of 89 HIV PrEP users in Bordeaux university hospital, Southwestern France.
Infections sexuellement transmissibles diagnostiquées chez 89 personnes suivies dans le programme PrEP du CHU de Bordeaux.

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

PrEP: HIV pre-exposure prophylaxis; 95% CI: 95% confidence interval.
[a] Detected in throat, first-void urine, or rectum.
[b] Incidence per 100 person-years.

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.

Disclosure of interest

The authors declare that they have no competing interest.

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References

[1] Cazanave C, Manhart LE, Bébéar C. *Mycoplasma genitalium*, an emerging sexually transmitted pathogen. Med Mal Infect 2012;42(9):381–92.
[2] Napierela Mavedzenge S, Weiss HA. Association of *Mycoplasma genitalium* and HIV infection: a systematic review and meta-analysis. AIDS 2009;23(5):611–20.
[3] Mavedzenge SN, Van Der Pol B, Weiss HA, Kwok C, Mambo F, Chipato T, et al. The association between *Mycoplasma genitalium* and HIV-1 acquisition in African women. AIDS 2012;26(5):617–24.
[4] Soni S, Alexander S, Verlander N, Saunders P, Richardson D, Fisher M, et al. The prevalence of urethral and rectal *Mycoplasma genitalium* and its associations in men who have sex with men attending a genitourinary medicine clinic. Sex Transm Infect 2010;86(1):21–4.
[5] Kojima N, Davey DJ, Klausner JD. Pre-exposure prophylaxis for HIV infection and new sexually transmitted infections among men who have sex with men. AIDS 2016;30(14):2251–2.
[6] Molina J-M, Charreau I, Spire B, Cotte L, Chas J, Capitant C, et al. Efficacy, safety, and effect on sexual behaviour of on-demand pre-exposure prophylaxis for HIV in men who have sex with men: an observational cohort study. Lancet HIV 2017;4(9):e402–10.
[7] Le Roy C, Pereyre S, Hénin N, Bébéar C. 2017 French prospective clinical evaluation of the Aptima *Mycoplasma genitalium* CE-IVD assay and macrolide resistance detection using three distinct assays. J Clin Microbiol 2017;55(11):3194–200.
[8] Le Roy C, Hénin N, Pereyre S, Bébéar C. Fluoroquinolone-resistant *Mycoplasma genitalium*, Southwestern France. Emerg Infect Dis 2016; 22(9):1677–9.
[9] Jensen JS, Cusini M, Gomberg M, Moi H. 2016 European guideline on *Mycoplasma genitalium* infections. J Eur Acad Dermatol Venereol 2016; 30(10):1650–6.
[10] Touati A, Peuchant O, Jensen JS, Bébéar C, Pereyre S. Direct detection of macrolide resistance in *Mycoplasma genitalium* isolates from clinical specimens from France by use of real-time PCR and melting curve analysis. J Clin Microbiol 2014;52(5):1549–55.
[11] Pereyre S, Laurier-Nadalié C, Bébéar C, for the investigator group. Mycoplasma genitalium and Trichomonas vaginalis in France: a point prevalence in people screened for sexually transmitted diseases. Clin Microbiol Infect 2017;23(2):122 [e1-122.e7].
[12] Tabrizi SN, Su J, Bradshaw CS, Fairley CK, Wlaker S, Tan LT, et al. Prospective evaluation of ResistancePlus MG, a new multiplex quantitative PCR assay for detection of *Mycoplasma genitalium* and macrolide resistance. J Clin Microbiol 2017;55(6):1915–9.
[13] Moi H, Horner PJ. 2016 European guideline on the management of non-gonococcal urethritis published. Euro Surveill 2016;21(22), http://dx.doi.org/10.2807/1560-7917.ES.2016.21.22.30248.
[14] Slifirski JB, Vodstrcil LA, Fairley CK, Ong JJ, Chow EPF, Chen MY, et al. *Mycoplasma genitalium* infection in adults reporting sexual contact with infected partners, Australia, 2008–2016. Emerg Infect Dis 2017; 23(11):1826–33.