SHORT REPORT

Prevalence of lymphogranuloma venereum among anorectal *Chlamydia trachomatis*-positive MSM using pre-exposure prophylaxis for HIV

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ABSTRACT

Objectives We evaluated the prevalence of lymphogranuloma venereum (LGV) in anorectal *Chlamydia trachomatis*-positive French men who have sex with men (MSM) using pre-exposure prophylaxis (PrEP) for HIV. Here, we describe the clinical, biological and behavioural characteristics of these patients.

Methods Laboratories throughout French metropolitan areas performing routine testing for *C. trachomatis* sent positive anorectal specimens to the National Reference Centre for bacterial STIs for LGV real-time PCR targeting the *pmp*H gene. Identification of the *C. trachomatis* genovar was performed by *omp*A gene sequencing. For each patient, clinical, biological and sexual behaviour data were collected after obtaining written informed consent.

Results In 2017, 486 anorectal *C. trachomatis*-positive specimens from MSM PrEP users were analysed. A strain of genovar L was detected in 91 cases (18.7%). Patients with LGV were significantly more symptomatic, had more sexual partners and more concurrent syphilis compared with their non-LGV counterparts. *Omp*A gene sequencing, successful in two-thirds of anorectal *C. trachomatis*-positive specimens, showed that the LGV cases were mainly of variant L2b (n=33), followed by genovar L2 (n=27) and genetic L2b *omp*A variants (n=16). In 11 cases, the results indicated the occurrence of genetic exchange between L and non-L genovars.

Conclusions LGV was diagnosed in 18.7% of anorectal *C. trachomatis*-positive specimens from French MSM using PrEP. LGV testing should be carried out for MSM diagnosed with chlamydia and with a large number of sexual partners, high-risk practices and anorectal symptoms. These patients should be presumptively treated as having LGV. This is the first surveillance study of LGV among MSM PrEP users and monitoring should continue.

INTRODUCTION

HIV pre-exposure prophylaxis (PrEP) is predominantly proposed to men who have sex with men (MSM) who are HIV-negative but at high risk of becoming infected with HIV. In France, the National Authority for Health approved the use of PrEP in January 2016. Several studies have reported that the use of PrEP is associated with an increased incidence of STIs, particularly rectal *Chlamydia trachomatis* infection.[1] In France, anorectal lymphogranuloma venereum (LGV) occurs primarily in HIV-positive MSM, whereas non-LGV cases occur primarily in HIV-negative MSM.[2] Because PrEP users are HIV-negative individuals who may have intercourse with HIV-positive individuals, we investigated LGV cases among anorectal *C. trachomatis*-positive MSM using PrEP in 2017.

METHODS

The diagnosis of LGV requires the confirmation of the L genovar in anorectal *C. trachomatis*-positive samples using a molecular approach.[3] Because these tests are not commercially available, our National Reference Centre (NRC) laboratory for STIs uses L-specific real-time simplex PCR assay.[3] Only the NRC performs this genotyping in France.

Laboratories throughout French metropolitan areas perform routine testing for the detection of *C. trachomatis* in anorectal specimens and then send positive specimens to the NRC for specific LGV real-time PCR analysis.[3] As soon as the result is available, the NRC invites the prescribing clinicians to complete a standardised questionnaire addressing demographic (gender, year of birth and city of residence), biological (HIV status and concurrent STIs), clinical (anal pain, tenesmus, discharge, bleeding, diarrhoea, anal pruritus and systemic symptoms (fever, weight loss, fatigue …)) and sexual behaviour (sexual orientation, number of sexual partners and probable sexual partner as a possible source of infection (casual, regular and sex worker)) data. The prescribing clinician obtains the patient's written informed consent and then sends the completed questionnaire to the NRC. This sentinel surveillance for anorectal *C. trachomatis* infections was approved by the country's Data Protection Authority.[2] For statistical analysis, Fischer's exact test or the χ^2 test was used for qualitative variables. A p value <0.05 was considered indicative of statistical significance.

RESULTS

In 2017, we received 558 anorectal *C. trachomatis*-positive specimens from MSM using PrEP. We excluded from the analysis 41 cases (7.3%) with an invalid LGV real-time PCR result and 31 duplicate cases. In total, 486 patients were included in the study. Most were from the Paris area (67.7%, 329/486), and the remainder (32.3%, 157/486)

were from other French cities. The mean age was 36.4 years (range 17–69 years). The return rate of clinical records was 81.5%. Overall, we received anorectal specimens from 30 hospitals and 10 STI screening centres from all of metropolitan France.

Using specific LGV real-time PCR targeting *pmp*H, an L-genovar strain was identified in 91 (18.7%) cases (LGV group) and a non-L-genovar strain in the remaining 395 (81.3%) subjects (non-LGV group). The mean age was similar in the two groups (table 1).

Symptoms were more common in patients with LGV (60.4%, 55/91) compared with their non-LGV counterparts (17.2%, 68/395) (p<0.001). The most frequent clinical manifestations in the LGV group were anal pain, tenesmus and discharge. Around two-thirds (56.4%, 31/55) of LGV patients presented with at least three different symptoms, whereas most non-LGV patients (63.2%, 43/68) reported only one or two clinical manifestations (p<0.001).

According to available data of sexual behaviour, the partner who was the possible source of infection was a casual sex partner in both groups. Nearly half of LGV patients (46.1%, 42/91) reported at least five different sexual partners in the previous month, compared with one-third of patients in the non-LGV group (32.1%, 127/395) (p=0.03). The prevalence of concurrent gonorrhoea was similar in the two groups (15.4%). Concurrent syphilis was more frequently diagnosed in the LGV group (14.3%, 13/91) than in the non-LGV group (5.3%, 21/395) (p=0.006).

Genovar determination was performed by amplifying and sequencing *omp*A gene directly from clinical specimens.[4] Among the 486 anorectal *C. trachomatis*-positive specimens, sequencing was successful in 299 cases (61.5%, 299/486) (table 1). An L-genovar strain was confirmed in 76 cases; 27 specimens had an *omp*A sequence identical to that of the *C. trachomatis* reference strain L2/434/Bu (GenBank accession no. AM884173.1) and 33 had an *omp*A sequence identical to the reference strain L2b/UCH-1/proctitis (GenBank accession no. AM884177.1). In the remaining 16 specimens, we identified three genetic L2b *omp*A variants. These results are in agreement with recent data on the French LGV outbreak.[5] A non-L-genovar strain was confirmed in 212 cases: 60 D/Da, 57 E, 51 G, 36 J, 5 F, 2 I/Ia and 1B. This distribution is similar to findings from MSM in Sweden.[6] Finally, in 11 cases, *pmp*H amplification and *omp*A sequencing yielded discordant genovar identifications, suggesting genetic exchange between L-genovars and non-L-genovars. Such strains have been described previously.[7]

Table 1 Characteristics of LGV and non-LGV anorectal infection among MSM using PrEP

	LGV cases n=91	Non-LGV cases n=395	
	n (%)	n (%)	P value
Age			
Mean (range)	37.8 (22-55)	36.1 (17-69)	0.11
Reported symptoms			**<0.001**
Yes	55 (60.4)	68 (17.2)	
No	25 (27.5)	248 (62.8)	
Not documented	11 (12.1)	79 (20)	
Clinical manifestations among patients reporting symptoms			
Anal pain	38 (69.1)	29 (42.6)	**0.003**
Tenesmus	34 (61.8)	21 (30.8)	**<0.001**
Anal discharge	27 (49)	19 (27.9)	**0.02**
Bleeding	21 (38.1)	16 (23.5)	0.08
Diarrhoea	12 (21.8)	19 (27.9)	0.44
Anal pruritus	7 (12.7)	19 (27.9)	**0.04**
Systemic symptoms	7 (12.7)	4 (5.9)	0.18
Not documented	6 (10.9)	9 (13.2)	
Number of clinical manifestations among patients reporting symptoms			**<0.001**
≤2	18 (32.7)	43 (63.2)	
>3	31 (56.4)	16 (23.5)	
Not documented	6 (10.9)	9 (13.2)	
Sexual partner			
Steady	0	9 (2.3)	
Casual	43 (47.3)	163 (41.3)	
Sex worker	0	1 (0.2)	
Not documented	48 (52.7)	222 (56.2)	
Number of sexual partners in the previous month			**0.03**
<5	8 (8.8)	56 (14.2)	
≥5	42 (46.1)	127 (32.1)	
Not documented	41 (45.1)	212 (53.7)	
Concurrent *N. gonorrhoeae*			0.6
Yes	14 (15.4)	61 (15.4)	
No	54 (59.3)	214 (54.2)	
Not documented	23 (25.3)	120 (30.4)	
Concurrent syphilis			**0.006**
Yes	13 (14.3)	21 (5.3)	
No	59 (64.8)	260 (65.8)	
Not documented	19 (20.9)	114 (28.9)	
*Omp*A gene sequencing result			
	27 L2	60 D/Da	
	33 L2b	57 E	
	16 L2b *omp*A variants	51 G	
	9 not amplifiable	36 J	
		5F	
		2 I/Ia	
		1B	
		178 not amplifiable	

Significant p values are in bold.
LGV, lymphogranuloma venereum; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis.

DISCUSSION

We report the first data on the prevalence of LGV among MSM PrEP users with an anorectal *C. trachomatis* infection. The centralised LGV genotyping allows the monitoring system to describe the biologically confirmed rectal LGV cases reliably in this population in France in 2017. We found that PrEP users with an LGV anorectal infection had the same characteristics as LGV patients before PrEP, regarding age, sexual behaviour, concurrent STIs and symptoms.[2 8] Our study has several limitations. First, the 81.5% return rate for the clinical questionnaire limited the case descriptions even if missing data were considered as responses and taken into account in the statistical analysis. Second, it would have been of interest to compare during the same period HIV-negative MSM using and not using PrEP. Unfortunately, this was not possible because the French surveillance network has since 2016 limited LGV testing to HIV-positive subjects or those with

rectal symptoms, as an observational study from 2010 to 2015 reported a significant association between LGV and these two clinical situations in France.[2] Nevertheless, from 2010 to 2015, LGV was diagnosed in 16.7% of HIV-negative MSM with an anorectal *C. trachomatis* infection, similar to our finding. Third, the duration of PrEP use was unknown, so we could not deduce whether previous risk behaviour before starting PrEP is at stake or whether risk behaviour is related to current use of PrEP.

Sentinel surveillance systems for LGV do not exist in many countries, and routine LGV testing of anorectal *C. trachomatis*-positive specimens is rare because of the absence of thoroughly validated nucleic acid amplification tests for LGV.[9] Recommendations on who to test are, therefore, limited by the availability of tests. Priority should be given to MSM PrEP users complaining of anorectal symptoms, with a large number of sexual partners in the last month or with concurrent syphilis. These patients should be presumptively treated for LGV. However, nearly 30% of PrEP users with LGV were asymptomatic, which was not observed in the sentinel surveillance between 2010 and 2015.[2] This result indicates that we should review the requirements for LGV testing in France and include MSM PrEP users as suggested by the European guidelines.[10]

We reported discordant results between *pmp*H gene amplification and *omp*A gene sequencing in 11 cases, suggesting the presence of 'recombinant' isolates. The possibility of two strains infecting the same host simultaneously increases the opportunities of genetic exchange between strains. This fact might result in the selection of new variants with greater virulence or more transmissibility.

In conclusion, LGV was diagnosed in 18.7% of cases. This is the first surveillance study of LGV among MSM PrEP users and monitoring should continue.

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