Trends in asymptomatic STI among HIV-positive MSM and lessons for systematic screening

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Abstract

The burden of STIs is particularly high in HIV-infected MSM patients. A recent increase in STIs prevalence has been noticed in the US and western European countries. We aim to assess trends in asymptomatic STIs following the publication of recommendations for STIs screening, i.e. Chlamydia (CT) and gonorrhea (NG). Seventeen centers located in the Paris area participated in the study. All asymptomatic HIV-infected MSM patients attending a follow up consultation were proposed to participated in the study. Asymptomatic patients were included over 2 periods: period 1 from April to December 2015 and period 2 from September to December 2017. Etiologic diagnosis of STIs including hepatitis B, C, syphilis, was performed using a serological test, including a non-treponemal titer with a confirmatory treponemal assay for syphilis. CT and NG were screened using a nucleic acid amplification test (NAATs) on 3 anatomical sites, i.e. urine, rectal and pharyngeal. Overall, 781 patients were included: 490 and 291 in periods 1 and 2 respectively. Asymptomatic CT, NG, and syphilis were diagnosed in 7.5%, 4.8% and 4.2% respectively. The rate of patients having a multi-site asymptomatic infection was 10.2% and 21.1% for CT and NG respectively. The most frequently involved anatomical sites for CT and NG asymptomatic infections were ano-rectal (66.1% and 55.2% respectively) and pharyngeal (47.4% and 60.5% respectively). CT and NG asymptomatic infection increased by 1.3- and 2-fold respectively between the two periods while syphilis decreased by 3 folds. Our results encourage to reconsider multisite screening for CT and NG in asymptomatic HIV positive MSM as the yield of screening
urinary samples only might be low. Despite the more systematic STI screening of asymptomatic HIV positive MSM the prevalence of STI is increasing in MSM in France. Therefore, this strategy has not led to alter CT and NG transmission. The decrease of syphilis might involve self-medication by doxycycline, and the intensification of syphilis screening.

Introduction

Sexually transmitted diseases (STIs) are a major public healthcare concern in sexually active patients and mostly in men who have sex with men (MSM) and HIV-positive patients. Trends in STIs prevalence are variable worldwide depending on health-care facilities, STIs prevalence, patient’s behavior, STI screening by providers, and STI treatment of infected persons and their partners [1, 2]. Furthermore, STI trends in HIV-positive MSM could have be influenced by the “undetectable = untransmittable” (U = U) campaigns. In high-income countries such as France, the burden of STIs is particularly high in MSM and HIV-infected patients [3, 4]. In France, some STIs such as lymphogranuloma venereum (LGV) are diagnosed almost exclusively in MSM, who represented 95% of all cases reported in 2016. MSM also accounted for 81% of early syphilis cases reported that same year. The number of syphilis cases raised by two-fold between 2010 and 2016, even if stability has been noticed between 2015 and 2016. Likewise, gonorrhea (NG) has increased by 127% between 2014 and 2016. Furthermore, a large outbreak of hepatitis A among MSM occurred in Europe in the middle of the 2010s [5, 6]. Moreover, the increased prevalence of STIs occurs in the context of recurrent shortages of medication such as the hepatitis A vaccine or Benzylpenicillin [5, 7].

Consequently, healthcare authorities have recently recommended screening for asymptomatic STI in all sexually active individuals and especially in MSM. NG and Chlamydia (CT) should be screened at 3 anatomical sites, i.e. urine, pharyngeal and anorectal, every 3 months [8–11].

In the context of the publication of European recommendations for STIs screening, the present study aimed at assessing the trends of asymptomatic STIs prevalence in HIV-positive MSM attending a routine HIV visit [10].

Materials and methods

This work is a part of the DRIVER project, a prospective multicentric project with two periods of inclusions designed to validate a STIs predictive score. It was approved by the French Ethics Committee (IDRCB 2014-A01358-39) and registered at ClinicalTrials.gov (ID number NCT02413632). Seventeen centers located in the Paris area participated in the study (Table 1). All HIV-positive MSM patients, attending their biannual follow-up visits, and able to respond to questionnaires in French were consecutively proposed to participate in the study. Symptomatic patients with STI clinical symptoms or skin rash were excluded. Patients were given a unique identifier and included over one of two periods: i) period 1 from April to December 2015 and; ii) period 2 from September to December 2017. All volunteers provided written informed consent.

STIs screening was performed as recommended by guidelines and manufacturer:

- a Nucleic Acid Amplification Test (NAAT) performed on 3 anatomical sites (first-catch urine sample, rectal swab, and pharyngeal swab) for NG and CT;
- a serological test including a non-treponemal (RPR or VDRL) and a treponemal test (TPHA or chemiluminescence assay detecting total antibody to *T. pallidum*) for syphilis. An incident
syphilis cases was considered in case of a new positivity or a 4-fold increase in the non-trep
nonemal title.

• serological tests for hepatitis B and C were retrieved from the patients’ records.

The NAAT and the serology were performed by the respective laboratories of each partici-
pant center. The laboratory technicians were blinded as to study participation.

CD4+ count and HIV viral load were assessed at the inclusion visit.

Socio-demographic and clinical data including age, sex, date of HIV diagnosis, past history
of STI, and sexual behavior were collected using a self-administered questionnaire as previ-
ously described [12].

Statistical analyses were performed using SSPS software (IBM, Armonk, United-States).
Categorical variables were compared using the Fisher’s exact test.

**Results**

**Patients’ characteristics**

Seventeen centers participated in the study, of which 13 and 16 included patients during the
first and the second period respectively (Table 1). Overall, 781 patients were enrolled: 490 dur-
ing the first period and 291 during the second one.

There were no significant differences in socio-demographic characteristics and sexual
behavior between patients included in each period (Table 2). Their median age was 47, with a
median duration of HIV-infection around 12 years (13.00 vs 11.55; \( P = 0.66 \)) and a CD4 +
count above 500/mm\(^3\) in around 75% (78.6% vs 74.1%; \( P = 0.22 \)). All patients were treated
by antiretrovirals (ARV) in group 1 versus 95.9% in group 2 (\( P < 0.01 \)). HIV viral load was not
detectable in 93.47% and 92.78% of the patients included in period 1 and 2 respectively
(\( P = 0.77 \)). The non-use of condom over the past 6 months was reported by 42.6% and 40.0%
of the patients included in periods 1 and 2 respectively (\( P = 0.68 \)).
Overall, 75.8% of all patients reported a previous history of STIs (Table 2). Most frequent STIs were syphilis (43.6%), anal condyloma (31.6%) and, NG (20.7%), while hepatitis A was reported by only 4.8%. The rate of patients reporting a previous history of STIs was significantly higher in period 1 than in period 2 (80.6% vs 67.7%; \( P < 0.01 \)) (Table 2). These trends are significant for 3 STIs: symptomatic hepatitis A (6.3% vs 2.4%; \( P = 0.02 \)), herpes (12.6% vs 5.1%; \( P < 0.01 \)) and anal condyloma (36.3% vs 27.1%; \( P < 0.01 \)). It almost achieved significance for NG (22.9% vs 17.2%; \( P = 0.06 \)). A similar but not significant trend was noticed for all other STI’s.

Chlamydia and gonorrhea

Overall, at least a bacterial STI (CT, NG or Syphilis) was diagnosed in 11.6% and 15.9% of all patients enrolled in period 1 and 2 respectively (\( P = 0.11 \)). Asymptomatic CT and NG were found in 7.5% and 4.8% of all patients respectively. For both CT and NG most of the patients had a single positive anatomical site (89.8% and 78.9% respectively), but a higher proportion of NG was recovered from 2 anatomical locations (CT: 13.6% vs NG: 21.0%; \( P < 0.01 \)) (Table 3). No pathogens were positive on three anatomical sites. Both CT and NG were mostly recovered from anorectal samples (CT: 66.1% vs NG: 55.3%; \( P = 0.38 \)) (Fig 1). NG was significantly more often present than CT in pharyngeal samples (CT: 30.5% vs NG: 60.5%; \( P < 0.01 \)). In contrast, CT was more frequently positive in urine samples (CT: 13.5% vs NG: 2.6%; \( P < 0.01 \)). Overall, CT was identified 5 and 2 times more often in anorectal and pharyngeal samples respectively than in urinary samples. NG was almost never isolated from urinary samples.

CT prevalence increased by 30% between periods 1 and 2. Anorectal and urinary samples tended to be more frequently positive in period 2 while the rate of positivity of pharyngeal samples decreased by 41%

### Table 2. Characteristics of patients, and history of reported STI.

|                      | First period (n = 490) | Second period (n = 291) | \( p \) |
|----------------------|------------------------|-------------------------|-------|
| Median age (years)   | 47 [40–54]             | 47 [39–55]              | 0.81  |
| Median duration of HIV infection (years) | 13 [5.91–22.30] | 11.55 [4.53–23.38] | 0.67  |
| Median CD4+ count    | 679 [526–894.75]      | 634 [497–820.5]        | 0.70  |
| Patient with CD4+ > 500/mm³ | 385 (78.57%)    | 217 (74.11%)             | 0.22  |
| HIV viral loads not detectable | 458 (93.47%) | 270 (92.78%)              | 0.77  |
| ARV treatment        | 490 (100%)            | 279 (95.9%)             | <0.01 |
| Median duration of ARV treatment (years) | 9.91 [4.26–17.97] | 8.36 [3.67–19.38] | 0.03  |
| History of STI       |                        |                         |       |
| • Hepatitis A        | 31 (6.3%)              | 7 (2.4%)                | 0.02  |
| • Herpes             | 62 (12.6%)             | 15 (5.1%)               | <0.01 |
| • Syphilis           | 220 (44.9%)            | 121 (41.6%)             | 0.37  |
| • C. trachomatis     | 56 (11.4%)             | 32 (11.0%)              | 0.85  |
| • N. gonorrhoeae     | 112 (22.9%)            | 50 (17.2%)              | 0.06  |
| • Proctitis          | 56 (11.4%)             | 28 (9.6%)               | 0.43  |
| • Condyoma           | 178 (36.3)             | 79 (27.1)               | <0.01 |
| • Anal condyoma      | 172 (35.1%)            | 75 (25.8%)              | <0.01 |
| • Genital condyoma   | 21 (4.3%)              | 11 (3.8%)               | 0.73  |
| • Buccal condyoma    | 3 (0.6%)               | 3 (1.0%)                | 0.68  |

### Sexual Behavior

- no use of condoms | 195 (42.6%) | 115 (40.0%) | 0.68
- Poppers use | 188 (39.6%) | 103 (35.9%) | 0.51
- Viagra® use | 84 (17.7%) | 47 (16.3%) | 0.51

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Overall, 75.8% of all patients reported a previous history of STIs (Table 2). Most frequent STIs were syphilis (43.6%), anal condyloma (31.6%) and, NG (20.7%), while hepatitis A was reported by only 4.8%. The rate of patients reporting a previous history of STIs was significantly higher in period 1 than in period 2 (80.6% vs 67.7%; \( P < 0.01 \)) (Table 2). These trends are significant for 3 STIs: symptomatic hepatitis A (6.3% vs 2.4%; \( P = 0.02 \)), herpes (12.6% vs 5.1%; \( P < 0.01 \)) and anal condyloma (36.3% vs 27.1%; \( P < 0.01 \)). It almost achieved significance for NG (22.9% vs 17.2%; \( P = 0.06 \)). A similar but not significant trend was noticed for all other STI’s.

Chlamydia and gonorrhea

Overall, at least a bacterial STI (CT, NG or Syphilis) was diagnosed in 11.6% and 15.9% of all patients enrolled in period 1 and 2 respectively (\( P = 0.11 \)). Asymptomatic CT and NG were found in 7.5% and 4.8% of all patients respectively. For both CT and NG most of the patients had a single positive anatomical site (89.8% and 78.9% respectively), but a higher proportion of NG was recovered from 2 anatomical locations (CT: 13.6% vs NG: 21.0%; \( P < 0.01 \)) (Table 3). No pathogens were positive on three anatomical sites. Both CT and NG were mostly recovered from anorectal samples (CT: 66.1% vs NG: 55.3%; \( P = 0.38 \)) (Fig 1). NG was significantly more often present than CT in pharyngeal samples (CT: 30.5% vs NG: 60.5%; \( P < 0.01 \)). In contrast, CT was more frequently positive in urine samples (CT: 13.5% vs NG: 2.6%; \( P < 0.01 \)). Overall, CT was identified 5 and 2 times more often in anorectal and pharyngeal samples respectively than in urinary samples. NG was almost never isolated from urinary samples.

CT prevalence increased by 30% between periods 1 and 2. Anorectal and urinary samples tended to be more frequently positive in period 2 while the rate of positivity of pharyngeal samples decreased by 41%.
samples tended to decrease. NG prevalence increased two-fold between the 2 periods of study. Anorectal location of NG was significantly more frequent during period 2 (4.47% vs 1.63%; \( P = 0.02 \)) and pharyngeal location also trends to increase between the two periods (5.24% vs 2.65%; \( P = 0.52 \)).

**Hepatitis B, hepatitis C, and syphilis**

Overall, 32 (4.1%) patients had chronic hepatitis B and 77 (9.8%) had a positive serology for hepatitis C (Table 3). Chronic hepatitis B prevalence remains stable between the two-period study (P1: 4.30% vs P2: 3.78%; \( P = 0.85 \)), while hepatitis C tended to decrease from 11.06% to 7.90% (\( P = 0.17 \)).

Overall, early syphilis was detected in 4.2% patients. Its prevalence fell from 5.71% to 1.68% between periods (\( P = 0.012 \)).

**Discussion**

The main finding of this work is a recent and rapid change in asymptomatic STIs prevalence among HIV-positive MSM living in the Paris area. Indeed, we report a significant decrease of syphilis prevalence and an increase in asymptomatic CT and of NG infections (which almost reach significance for the latter).

CT is the main STI in the general population in France. Its prevalence is increasing in all categories of the population [3]. However, 2 findings characterized MSM: i) serovar L causing *Lymphogranuloma venerum* (LGV), an emerging infectious disease in Western Europe and North America, is almost exclusively found in this population [3, 13], nevertheless, CT serovar

| Table 3. Asymptomatic co-infection screened at inclusion. |
|------------------------------------------------------------|
|               | First period (n = 490) | Second period (n = 291) | P      |
|----------------|------------------------|-------------------------|--------|
| **Hepatitis B**| 21 (4.30%)             | 11 (3.78%)              | 0.85   |
| **Hepatitis C**| 54 (11.06%)            | 23 (7.90%)              | 0.17   |
| **Active syphilis** | 28 (5.71%)           | 5 (1.68%)               | **0.01** |
| **C. trachomatis** | 33 (6.73%)           | 26 (8.96%)              | 0.27   |
| **Nb of site of isolation**                              |                        |                        |        |
| • 1 location    | 29 (87.8%)             | 24 (92.3%)              | 0.24   |
| • 2 locations   | 4 (12.2%)              | 2 (7.7%)                | 1      |
| • 3 locations   | 0                      | 0                       |        |
| **Site of isolation**                                   |                        |                        |        |
| • urine         | 3 (0.61%)              | 5 (1.72%)               | 0.16   |
| • pharynx       | 14 (2.86%)             | 4 (1.37%)               | 0.22   |
| • ano-rectal    | 20 (4.08%)             | 19 (6.52%)              | 0.17   |
| **N. gonorrhoeae**                                     | 18 (3.67%)             | 20 (6.89%)              | 0.06   |
| **Nb of site of isolation**                             |                        |                        |        |
| • 1 location    | 15 (83.3%)             | 15 (75.0%)              | 0.18   |
| • 2 locations   | 3 (16.7%)              | 5 (25.0%)               | 0.16   |
| • 3 locations   | 0                      | 0                       |        |
| **Site of isolation**                                   |                        |                        |        |
| • urine         | 0                      | 1 (0.34%)               | 0.37   |
| • pharynx       | 13 (2.65%)             | 10 (5.24%)              | 0.52   |
| • ano-rectal    | 8 (1.63%)              | 13 (4.47%)              | 0.02   |
| **At least a bacterial STI**                            | 11.6%                  | 15.9%                   | 0.11   |

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were not identified in the present study. And; ii) pharyngeal and anorectal asymptomatic infection are more frequent than asymptomatic urinary infections [14–17].

Multisite screening might enhance the identification of asymptomatic CT infected patients. However, in the present study, the 3 anatomical sites display a variable rate of positivity, urinary samples being the least frequently positive sample. In a monocentric study in Germany involving 296 asymptomatic HIV-positive MSM, CT was detected in 7.3%, 1.7% and 1.0% of anorectal, pharyngeal and, urethral samples respectively [14]. NG was detected in 4.5%, 2.0% and, 1.4% respectively. de Vrieze et al. reported a CT prevalence of 3.32% and 8.30% in urethral and anorectal specimens of MSM attending a STI clinic in Amsterdam [15]. However, some of these patients were symptomatic. In France, CT prevalence in pharyngeal, anorectal, and urine samples was assessed to 1%, 8% and, 3% in a cohort of 116 MSM (of which 99 HIV-positive) living in Paris area [16]. In contrast, the rate of positivity of urethral samples reaches 29.1% in a cohort of 346 asymptomatic MSM living in Thailand (versus 17.6% and

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Fig 1. Repartition of anatomical sites positive for *C. trachomatis* and *N. gonorrhoae*. Site of isolation of *C. trachomatis* during period 1 (a.) and 2 (b.) and *N. gonorrhaea* during period 1 (c.) and 2 (d.).

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17.0% for pharyngeal and anorectal samples respectively) [18]. This suggests that, screening strategies should perhaps be adapted regarding local epidemiology. Considering that asymptomatic patients have a low rate of positive urinary samples in comparison to anorectal and pharyngeal samples, our results suggest stopping the screening of CT and NG in urinary samples in France and other western European countries with similar prevalence of CT and NG [17].

Furthermore, three anatomical site screening of CT and NG for asymptomatic STI was implemented in all centers at the beginning of the study. The relatedness between the increased prevalence of both CT and NG in period 2 and the implementation of multisite screening remains to be determined. Despite the patients enrolled in periods 1 and 2 were different, a change in patients’ risk behavior, which could explain a rise in STIs prevalence, was not found, e.g. the rate of condom use was not different, 43% in the period 1 and 40% period 2 ($p = 0.68$). One objective of the strategy of systematic screening of asymptomatic STI recommended by WHO and local Health-care authority was to reduce STIs transmission [8, 10, 19]. However, there is no evidence that this strategy reduces the transmission of these pathogens [20]. And, as for some pathogens such as *N. meningitidis*, we could hypothesis that carriage strains are genetically different from infectious strains [21]. Further studies are therefore needed in order to understand the potential pathogenic role of asymptomatic strains and also the possible quantitative role of infectious pathogen load in the occurrence of symptoms. As a consequence of systematic screening, antibiotics use is increasing in the sexually active population, leading to a potential impact on micro-organisms resistance [22]. Consequently, the risks and benefits of CT and NG screening should be assessed having in mind the large use of antibiotics in the sexually active population.

Surprisingly, syphilis prevalence fell 3-fold between the 2 periods of study. This trend is opposite to most reports. In France, syphilis reported cases have consistently increased since the early 2000s [1, 3, 23] though the prevalence of early infection remained stable between 2015 and 2016 [3]. The significant opposite trend reported in the present cohort of HIV-positive MSM patients could be explained by enrollment bias. First, one third of patients were included in period 2 by 4 centers that had not participated in period 1. Then, a previous history of STI was more frequently reported by patients enrolled in period 1. However, CT and NG prevalence increased as expected. Therefore, both biases would probably have no impact on syphilis prevalence. As a similar rate of patients included in periods 1 and 2 reported a previous history of syphilis, it is unlikely that immunity factors could explain such a difference in active syphilis rate—besides, it is common knowledge that previous syphilis does not induce protective immunity against re-infection. Over the past decade, the salient features of the evolution in syphilis prevalence were related to change in: i) the perception of sexual risk, ii) the diagnosis and immediate treatment of HIV (Treatment as Prevention or TasP) and other STIs and, iii) perception of sexual behavior risk [24–27]. PrEP for HIV prevention, has been in use for several years, and, recently a similar strategy using doxycycline has been assessed to prevent bacterial [28, 29]. Doxycycline PrEP was associated with a significant reduction in syphilis and CT but not NG in HIV− MSM on PrEP, and studies are currently being conducted to evaluate the impact on STIs in HIV+ MSM and to confirm the results in HIV− MSM on PrEP. It may be hypothesized therefore that some patients could have taken antibiotics to prevent STIs even in the absence of recommendations. Indeed, in the United-Kingdom, in 106 patients followed at an HIV Prep consultation, 8% self-medicated with antibiotics in order to prevent bacterial STIs [30]. Such could have been the case for patients enrolled in period 2 (though our study’s design did not allow us to investigate this issue).

STIs are still of major health concern in HIV-positive MSM, but several recent changes in their prevalence are occurring. Today, it is demonstrated that there is no risk of transmission of HIV from an HIV-positive person with consistent undetectable viral load to an HIV
negative person during sexual intercourse, regardless of gender or sex. This treatment as prevention (TasP) message has been a part of a public campaign as “undetectable = untransmittable” (U = U) [31, 32]. For the French HIV positive MSM, ‘having a sexual partner’ and condomless sex, both increased in frequency between 2000 and 2017 [33]. The NG prevalence are increasing in this population and anorectal and pharyngeal sites are probably a major reservoir of these pathogens. These results encourage to review the current strategy of multi-site screening by stopping considering urine samples or even to stop performing CT and NG screening. Molecular and serological characterization will perhaps provide more insight into CT and NG natural history, pathogenesis and transmission.

Our study might not be representative of HIV-positive MSM as all patients enrolled lived in the Paris area. We could not exclude the screening recommendations are followed by all centers in France. Furthermore, some clinics only participated in one of the 2 time periods, and a small number of patients were enrolled from some others. Sexual behavior and antibiotic consumption in the past previous year could probably reveal another insight into the trend of STI prevalence in HIV-positive MSM.

Conclusion

In conclusion, in asymptomatic HIV positive MSM attending their routine consultation in Paris area, a systematic screening reveals a bacterial asymptomatic STI in at least 11% of the patients. Our results encourage to reconsider the interest of systematic multisite screening for CT and NG in asymptomatic patients as the positive screening in urinary samples are low and this systematic screening has not led to disrupt CT and NG transmission. Assessing the impact of the current strategy of STIs screening is therefore needed. On the contrary, the prevalence of asymptomatic syphilis has decreased between 2015 and 2017. The reasons for this change are probably multifactorial involving self-medication by doxycycline, implementation, and generalization of active screening in the middle 2010s.

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**References**

1. Ndeikoundam Ngangro N, Viriot D, Lucas E, Boussac-Zarebska M, Lot F, Dupin N, et al. Relevance of health care reimbursement data to monitor syphilis epidemic: an alternative surveillance through the national health insurance database in France, 2011–2013. BMJ Open. 2018; 8: e020336. https://doi.org/10.1136/bmjopen-2017-020336 PMID: 30037863

2. Kularatne RS, Nil R, Rowley J, Kufa-Chakezha T, Peters RPH, Taylor MM, et al. Adult gonorrhea, chlamydia and syphilis prevalence, incidence, treatment and syndromic case reporting in South Africa: Estimates using the Spectrum-STI model, 1990–2017. PLoS One. 2018; 13: 1–22. https://doi.org/10.1371/journal.pone.0205863 PMID: 30321236

3. Ngangro NN, Viriot D, Fournet N, Pioche C, De Barbeyrac B, Goubard A, et al. Bacterial sexually transmitted infections in France: Recent trends and patients’ characteristics in 2016. Eurosurveillance. 2019; 24. https://doi. org/10.2807/1560-7917.ES.2019.24.5.1800038 PMID: 30722812

4. Farfour E, Dimi S, Majerholc C, Fourn E, Séne T, Chaida MB, et al. Increase in sexually transmitted infections in a cohort of outpatient HIV-positive men who have sex with men in the Parisian region. Médicine Mal Infect. 2017; 47: 490–493. https://doi.org/10.1016/j.mea ml.2017.06.004 PMID: 28943174

5. Zucman D, Farfour E, Mazaux L, Hillaire S, Dimi S, Lesprit P, et al. How to face the outbreak of viral hepatitis a in men who have sex with men in France without vaccines? Clin Infect Dis. 2017; 65: 1053–1054. https://doi.org/10.1093/cid/cix458 PMID: 28510643

6. Beebeejaun K, Degala S, Balogun K, Simms I, Woodhall SC, Heinsbroek E, et al. Outbreak of hepatitis A associated with men who have sex with men (MSM), England, July 2016 to January 2017. Euro Surveill. 2017;22. https://doi.org/10.2807/1560-7917.ES.2017.22.5.30454 PMID: 28183392

7. Dhanani A, Parent du Chatellet I, Ioughlissen S, Maison P. [Supply disruptions and drug shortages: the example of benzathine benzylpenicillin]. Rev Prat. 2018; 68: 849–854. Available: http://www.ncbi.nlm.nih.gov/pubmed/3069447 PMID: 3069447

8. Haute Autorité de Santé. Réévaluation de la stratégie de dépistage des infections à Chlamydia trachomatis. 2018.

9. Workowski KA, Bolan GA, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm reports Morb Mortal Wkly report Recomm reports. 2015; 64: 1–137. Available: http://www.ncbi.nlm.nih.gov/pubmed/26042815

10. ECDC. Preventing HIV and STI among men who have sex with men—an ECDC guidance. 2015.

11. Haute Autorité de Santé. Évaluation des tests d’amplification des acides nucléiques (TAAN) recherchant Neisseria gonorrhoeae. 2015 [cited 23 Nov 2019]. Available: https://www.has-sante.fr/jcms/c_2035591/fr/evaluation-des-tests-d-amplification-des-acides-nucleiques-taann-recherchant-neisseria-gonorrhoeae

12. Kalichman SC, Johnson JR, Adair V, Rompa D, Multhau K, Kelly JA. Sexual Sensation Sensing: Scale Development and Predicting AIDS-Risk Behavior Among Homosexually Active Men. J Pers Assess. 1994; 62: 385–397. https://doi.org/10.1207/s15327752jpa6203_1 PMID: 8027807

13. Vargas-Leguas H, Oialla PG de, Arando M, Armentol P, Barberà MJ, Vail M, et al. Lymphogranuloma venereum: a hidden emerging problem, Barcelona, 2011. Eurosurveillance. 2012; 17: 20057. https://doi.org/10.2807/ese.17.02.20057-en PMID: 22264862

14. Spinner CD, Boesecke C, Jordan C, Wyen C, Kümmerle T, Knecht G, et al. Prevalence of asymptomatic sexually transmitted infections in HIV-positive men who have sex with men in Germany: results of a multicentre cross-sectional study. Infection. 2018; 46: 341–347. https://doi.org/10.1007/s15010-018-1124-6 PMID: 29460228

15. Vrieze NHN de, Versteeg B, Bruisten SM, Rooijen MS van, Helm JJ van der, Vries HJC de. Low Prevalence of Urethral Lymphogranuloma Venereum Infections Among Men Who Have Sex With Men: A
Asymptomatic STI among HIV-positive MSM

16. Philibert P, Khiri H, Pénaranda G, Camus C, Drogoul M-P, Halfon P. High Prevalence of Asymptomatic Sexually Transmitted Infections among Men Who Have Sex with Men. J Clin Med. 2014; 3: 1386–91.

17. Voirin N, Allam C, Charre C, Fernandez C, Godinot M, Oria F, et al. Optimizing Strategies for Chlamydia trachomatis and Neisseria gonorrhoeae Screening in Men Who Have Sex With Men: A Modeling Study. Clin Infect Dis. 2019 [cited 3 Dec 2019]. https://doi.org/10.1093/cid/ciz510 PMID: 3119933

18. Hinkan S, Chuerduangphui J, Ekalaksananan T, Budkaew J, Proyrungroj K, Pimson C, et al. Anatomical site distribution and genotypes of Chlamydia trachomatis infecting asymptomatic men who have sex with men in northeast Thailand. Int J STD AIDS. 2018; 29: 842–850. https://doi.org/10.1177/0956462418760659 PMID: 2915461

19. Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recommendations and Reports. 2015. https://doi.org/10.1111/j.1746-1561.1994.tb03287.x PMID: 26042815

20. Tsoumanis A, Hens N, Kenyon CR. Is Screening for Chlamydia and Gonorrhoea in Men Who Have Sex With Men Associated With Reduction of the Prevalence of these Infections? A Systematic Review of Observational Studies. Sex Transm Dis. 2018; 45: 615–622. https://doi.org/10.1097/OLQ.0000000000000824 PMID: 29485537

21. Bille E, Meyer J, Jamet A, Euphrasie D, Barnier J-P, Brissac T, et al. A virulence-associated filamentous bacteriophage of Neisseria meningitidis increases host-cell colonisation. Shafer WM, editor. PLOS Pathog. 2017; 13: e1006495. https://doi.org/10.1371/journal.ppat.1006495 PMID: 28704569

22. Durukan D, Read TRH, Murray G, Doyle M, Chow EPF, Vodstrcil LA, et al. Resistance-guided antimicrobial therapy using doxycycline-moxifloxacin and doxycycline-2.5g azithromycin for the treatment of Mycoplasma genitalium infection: efficacy and tolerability. Clin Infect Dis. 2019 [cited 10 Nov 2019]. https://doi.org/10.1093/cid/ciz1031 PMID: 31629695

23. Pratas AC, Goldschmidt P, Lebeaux D, Aguilar C, Ermak N, Benesty J, et al. Increase in Ocular Syphilis Cases at Ophthalmologic Reference Center, France, 2012–2015. Emerg Infect Dis. 2018; 24: 193–200. https://doi.org/10.3201/eid2402.171167 PMID: 29350138

24. Putot A, Rozé B, Pierre-François S, Pircher M, Vilain R, Benesty J, et al. Increase in Ocular Syphilis Cases at Ophthalmologic Reference Center, France, 2012–2015. Emerg Infect Dis. 2018; 24: 193–200. https://doi.org/10.3201/eid2402.171167 PMID: 29350138

25. Kahn RH, Heffelfinger JD, Berman SM. Syphilis outbreaks among men who have sex with men: a public health trend of concern. Sex Transm Dis. 2002; 29: 285–7. https://doi.org/10.1097/00007435-200205000-00006 PMID: 11984445

26. Brewer TH, Peterman TA, Newman DR, Schmitt K. Reinfections during the Florida syphilis epidemic, 2000–2008. Sex Transm Dis. 2011; 38: 12–7. https://doi.org/10.1097/OLQ.0b013e3181e9afc7 PMID: 20739912

27. Stall RD, Hays RB, Waldo CR, Ekstrand M, McFarland W. The Gay ‘90s: a review of research in the 1990s on sexual behavior and HIV risk among men who have sex with men. AIDS. 2000; 14 Suppl 3: S101–14. Available: http://www.ncbi.nlm.nih.gov/pubmed/11066853 PMID: 11066853

28. Molina J-M, Charreau I, Spire B, Coutte 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: e402–e410. https://doi.org/10.1016/S2352-3018(17)30089-9 PMID: 28747274

29. Molina J-M, Charreau I, Chidiac C, Pialoux G, Cua E, Delaugerre C, et al. Post-exposure prophylaxis with doxycycline to prevent sexually transmitted infections in men with sex with men: an open-label randomised sub-study of the ANRS IPERGAY trial. Lancet Infect Dis. 2018; 18: 308–317. https://doi.org/10.1016/S1473-3099(17)30725-9 PMID: 29229440

30. Carveth-Johnson T, Stingone C, Nwokolo N, Whitlock G. Doxycycline use in MSM taking PrEP. Lancet HIV. 2018; 5: e482. https://doi.org/10.1016/S2352-3018(18)30210-8 PMID: 30213546

31. Rodger AJ, Cambiano V, Bruun T, Vernazza P, Collins S, van Lunzen J, et al. Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy. JAMA. 2016; 316: 171. https://doi.org/10.1001/jama.2016.5148 PMID: 27404185

32. Rodger AJ, Cambiano V, Bruun T, Vernazza P, Collins S, Degen O, et al. Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study. Lancet (London, England). 2019; 393: 2428–2438. https://doi.org/10.1016/S0140-6736(19)30418-0 PMID: 31056293
33. Champenois K, Seng R, Persoz A, Essat A, Gaud C, Laureillard D, et al. Calendar trends in sexual behaviours in a cohort of HIV-infected MSM at the era of treatment as prevention of HIV infection. AIDS. 2018; 32: 1871–1879. https://doi.org/10.1097/QAD.0000000000001916 PMID: 29927787