Journal of Virus Eradication 8 (2022) 100065

Contents lists available at ScienceDirect

Journal of Virus Eradication

journal homepage: www.sciencedirect.com/journal/journal-of-virus-eradication

Original research

A cohort analysis of sexually transmitted infections among different groups of men who have sex with men in the early era of HIV pre-exposure prophylaxis in France

Christina K. Psomas [a,*], Guillaume Penaranda [b], Frederique Retornaz [a], Hacene Khiri [b], Marion Delord [a], Philippe Halfon [a,b,1], Patrick Philibert [a,1]

[a] Department of Infectious Diseases and Internal Medicine, European Hospital of Marseille, Marseille, France
[b] Laboratoire Alphabio, European Hospital of Marseille, Marseille, France

ARTICLE INFO

Keywords:
PrEP
Sexually transmitted infections
Men who have sex with men
HIV
Prevention
Monitoring

ABSTRACT

Background: MSM are at particular risk of STIs due to sexual behavior and substance use. HIV PrEP use may increase this risk.
Design: Our aim was to comparatively assess incident STIs among different at-risk groups—PLWHIV, HIV-negative PrEP and no-PrEP users—seen at our center early after PrEP implementation.
Methods: Clinical data were retrospectively collected on 636 MSM seen at the Infectious Diseases Department between September 2016 and October 2018. STI incidence rate was assessed among groups for the whole period, as well as separately for each year of the study.
Results: Overall STI incidence rate ratio was higher in HIV-neg when compared to PLWHIV. In multivariate analysis, STI risk was significantly higher among HIV-neg no-PrEP users compared to PLWHIV, while not different between PLWHIV and PrEP users.
STI incidence globally increased during the first 2 years after PrEP approval among PLWHIV and no-PrEP users, stated by odds ratio (OR = 1.77 [1.23–2.55], p = 0.0020 and OR = 2.29 [0.91–5.73], p = 0.0774 respectively) while it remained rather stable for HIV-neg PrEP users (OR = 1.19 [0.60–2.38], p = 0.6181). The HIV-neg no-PrEP group remained at higher risk of STI than PLWHIV and PrEP users during the two periods.
Conclusion: These results suggest that a proactive approach of an efficient follow-up of MSM participants since PrEP approval may have prevented an increase of the incidence of STIs among PrEP users.

1. Introduction

After decades of progress at reducing sexually transmitted infections (STIs), the industrial countries are seeing a dramatic reversal of fortunes. Indeed, the CDC has documented sharp increases in the number of cases of chlamydia, gonorrhoea, and syphilis since 2013.[1,2] This high incidence of STI is mainly linked to sexual behavior changes of men who have sex with men (MSM), especially regarding condomless sex and use of recreational drugs.[3–5] Approved by the Food and Drug Administration (FDA) in 2012, the use of oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) as HIV pre-exposure prophylaxis (PrEP) was approved in France as of January 4, 2016, first within the Temporary Recommendation for Use (TRU) protocol framework, and almost a year later with a facilitated access in hospitals and GP's offices. Although PrEP reduces the risk of HIV transmission in adherent high-risk individuals by more than 90%, long-term data are just beginning to accumulate regarding consequences of PrEP to HIV transmission, incidence of STI, and links to primary care of MSM.[6] Indeed, the full story regarding PrEP may be more complicated and nuanced, since MSM are not equally likely to be prescribed PrEP. Moreover, the relationship between HIV and other STIs among high-risk groups is complex. The STI burden of disease is high worldwide.[7,8] Finally, there is general concern that use of PrEP may lead to increased incidence of STI, especially in the context of ChemSex and substance use.[9,10] It is therefore crucial to multiply epidemiological data in order to assess STI incidence in the context of the PrEP era and carefully evaluate PrEP effects on public

* Corresponding author. European Hospital of Marseille, 6 Désirée Clary Street, 13003, Marseille, France.
E-mail address: C.PSOMAS@hopital-europeen.fr (C.K. Psomas).
[1] contributed equally to the study.

https://doi.org/10.1016/j.jve.2022.100065
Received 8 December 2021; Received in revised form 7 February 2022; Accepted 22 February 2022
Available online 24 February 2022

health since its implementation. The purpose of the present cohort study was to assess incident STIs in different MSM populations. We comparatively evaluated STI incidence among different at-risk groups of MSM participants [PLWHIV, HIV-negative PrEP (HIV-neg) users and HIV-neg no-PrEP users] during the first two years after PrEP implementation in France.

2. Methods

2.1. Population and settings

This study was conducted on data collected retrospectively on 636 MSM regarding STI (chlamydia, gonorrhoea, mycoplasma, syphilis, HIV, hepatitis A and C) incidence rate in the period between September 2016 and October 2018. Participants were followed up in the Infectious Diseases Department of the European Hospital of Marseille (France) in the context of HIV, PrEP treatment or regular follow-up for HIV-neg no-PrEP participants having a history of STI, namely on a 3-month basis for HIV-neg PrEP users, and on a 4- to 6-month basis for PLWHIV and HIV-neg no-PrEP participants. Follow-up visits systematically included STI prevention strategies (such as counseling and condoms).

According to French regulations, the study was registered as a reference methodology (MR-004) on the Health Data Hub French registering website platform (https://www.health-data-hub.fr). Information was given to all patients for being included in the study.

Chlamydia, gonorrhoea, mycoplasma, syphilis, HIV, hepatitis A and C were systematically screened for using standard methods, namely, validated serology tests for syphilis, HIV, hepatitis A and C; and molecular biology methods for the organisms Chlamydia trachomatis, Neisseria gonorrhoea, and Mycoplasma genitallium (polymerase chain reaction, or PCR, performed on anal swabs, throat swabs, and urine samples). Each time STI screening was positive, a specific treatment was proposed according to the French STI treatment guidelines.

The STI incidence rate (IR) and incidence rate ratio (IRR) [95% CI] were assessed among the 3 groups of patients for the whole two-year period (P), and IRR was also evaluated separately for the first period (P1: September 2016–September 2017) and second period (P2: October 2017–October 2018) of the study.

2.2. Statistical analysis

Continuous data were reported using median and interquartile range (IQR); qualitative data were reported using frequencies and percentages. The Kruskal-Wallis test was used to compare age among groups (PLWHIV, HIV-neg PrEP users, and HIV-neg no-PrEP users). The multiple comparison Tukey test was used to compare frequencies of STIs among groups. STI IRs and their 95% CI were assessed assuming a Poisson distribution. The follow-up duration was calculated for each patient to assess the person-years (PY) statistic. Crude comparisons of overall STI risk among groups were expressed using an OR with their 95% CI. Multivariate logistical regressions were assessed to compare overall STI risk ratio, sites of infection, and type of infections among groups after adjusting for age and number of visits. To compensate for family-wise error rate, a Bonferroni correction for multiplicity of secondary endpoints analyses of STI risk factors was applied (sites of infection analyses, type of infections analyses, and longitudinal analysis): alpha level was corrected to 0.006.

All tests were two-sided. Calculations were performed using SAS V9.4 software (SAS Institute Inc., Cary, NC).

3. Results

3.1. Characteristics of participants

Detailed characteristics of participants are described in Table 1. Overall, a total of 636 individuals were enrolled (September 1, 2016–October 30, 2018). This number of individuals corresponded to 2526 medical visits (including treatment visits), of whom 447 were PLWHIV. Among 189 HIV-neg individuals, 105 were on PrEP. The median age of PLWHIV was 48.7 years (IQR 39.5–55.8), 36.6 years (29.6–44.5) among PrEP users, and 40.3 years (30.4–50.1) among HIV-Neg no-PrEP users (Kruskal-Wallis p = <0.0001). PLWHIV were all on effective ART (more than 95% had a plasma HIV viral load of less than 20 copies/mL) and had a satisfactory immune reconstitution status of CD4 T cell count >500/mm3. 152 men (24%) were ≤35 years of age.

Table 1
Characteristics of patients.

	PLWHIV	HIV-neg PrEP	HIV-neg no-PrEP
Number of Participants	447	105	84
Median age (years) (IQR)	48.7 (39.5–55.8)	36.6 (29.6–44.5)	40.3 (30.4–50.1)
Number of medical visits	1866 (74%)	471 (19%)	191 (7%)
Median number of visits/ patient (IQR)	5 (3–5)	4 (4–6)	2 (1–3)
Number of STIs (%)	134 (30%)	42 (40%)	37 (44%)
- **HIV (%)**	0	0	10 (11.9%)
- **HAV (%)**	10 (2.2%)	4 (3.8%)	4 (4.8%)
- **HCV (%)**	15 (3.4%)	3 (2.9%)	0
- **Gonorrhoae (%)**	45 (10.1%)	24 (22.9%)	6 (7.1%)
- **Chlamydia infections (%)**	32 (7.2%)	18 (17.1%)	11 (13.1%)
- **Mycoplasma infections (%)**	25 (5.6%)	9 (8.6%)	5 (6.0%)
- **Syphilis infections (%)**	33 (7.4%)	8 (7.6%)	8 (9.5%)
Participants with ≧ 2 STIs (%)	28 (21%)	21 (50%)	8 (22%)

3.2. STIs risk

Over the complete study follow-up period of two years, STI IR was significantly higher in the HIV-neg no-PrEP users' group (IR: 41.6 [29.3–57.3] per 100 patient-years [PY]) compared to PLWHIV (IR:17.7 [14.9–21.0] per 100 PY) (p<.0001). STI IR was higher in HIV-neg no-PrEP users compared to HIV-neg PrEP users (IR:26.3 [18.9–35.5] per 100 PY), as well as in HIV-neg PrEP users compared to PLWHIV, but these differences were not statistically significant.

Crude comparisons showed that overall STI risk was significantly higher for PreP users and HIV-neg no-PrEP users than for PLWHIV (OR 1.56 [1.00–2.42] p = 0.0484, and 1.84 [1.14–2.96] p = 0.0121 respectively) (Table 2). PreP users tended to have a lower risk of STIs than HIV-neg no-PreP users (p = 0.5751).

In multivariate analysis, after adjustment for age (≤35 vs. >35 years) and for the number of screening visits, STI risk was not significantly different between PLWHIV and PrEP users (p = 0.3094) (Table 2); in this analysis we confirmed that STI risk was significantly higher among HIV-neg no-PrEP users compared to PLWHIV, and to PreP users (p < 0.0001 for both comparisons).

Table 2
Unadjusted and adjusted OR of STIs risk among groups of MSM.

	Unadjusted OR [95%CI] – (p)	Multivariate[a] OR [95% CI] (p)
Group		
HIV-neg PrEP vs. PLWHIV	1.56 [1.00–2.42] (0.0484)	1.30 [0.79–2.15] (0.3094)
HIV-neg no-PrEP vs. PLWHIV	1.84 [1.14–2.96] (0.0121)	5.02 [2.78–9.03] (<.0001)
HIV-neg PrEP vs. HIV-neg no-PrEP	0.85 [0.47–1.52] (0.5751)	0.26 [0.13–0.52] (<.0001)
Age >35 vs. ≤35	0.81 [0.55–1.18] (0.2698)	0.67 [0.43–1.05] (0.0802)

[a] Adjusted for the number of visits.

Quantitative analysis of STI site of infection suggested that PrEP users and HIV-neg no-PrEP users were more at risk of a urethral STI compared to PLWHIV, while there was no statistical difference among the HIV-neg populations (Table 3). No statistical difference was shown among groups regarding rectal and pharyngeal sites of STIs, apart for pharyngeal STIs in PrEP users compared to PLWHIV (OR 3.34 [1.46–7.66], p = 0.0044).

Analysis of the types of bacterial STIs showed that gonorrhoea was significantly more frequent among PrEP users compared to PLWHIV (OR 2.67 [1.45–4.91], p = 0016), while this infection was not significantly different between other groups (Table 4). There were significantly more chlamydia infections in HIV-neg no-PrEP users compared to PLWHIV (OR 4.27 [1.70–10.73], p = 0.0020), while a marginal difference was observed between PrEP users and PLWHIV (OR 2.31 [1.16–4.58], p = 0.0167), and no difference was observed between PrEP-users and no-PrEP users (OR 0.54 [0.19–1.54], p = 0.2482) (Table 4). No statistical difference was shown between groups for mycoplasma infections, while there were slightly more syphilis cases in HIV-neg no-PrEP users compared to PLWHIV (OR 2.70 [1.08–6.76], p = 0.0345), but no difference between other groups.

The number of participants having presented ≧ 2 STIs was significantly higher among PrEP users when compared to PLWHIV and to HIV-neg no-PrEP users (50% vs 21% and 22% respectively, Tukey test for multiple comparisons p < 0.05), but there was no significant difference between HIV-neg no-PrEP users and PLWHIV (22% vs. 21% respectively).

Table 3
STI risks for the different sites of STIs.

Group	Urethral Site Multivariate[a] OR [95%CI] (p)
HIV-neg PrEP vs. PLWHIV	2.85 [1.50–5.43] (0.0014)
HIV-neg no-PrEP vs. PLWHIV	3.89 [1.58–9.61] (0.0032)
HIV-neg PrEP vs. HIV-neg no-PrEP	0.73 [0.27–1.99] (0.5400)
PLWHIV *Age >35 vs. ≤35*	0.85 [0.31–2.32] (0.7456)
HIV-neg PrEP Age >35 vs. ≤35	2.05 [0.68–6.21] (0.2030)
HIV-neg no-PrEP Age >35 vs. ≤35	0.35 [0.09–1.28] (0.1117)
Age≤*35*	
HIV-neg PrEP vs. PLWHIV	1.46 [0.40–5.36] (0.5707)
HIV-neg no-PrEP vs. PLWHIV	7.66 [2.05–28.70] (0.0025)
HIV-neg PrEP vs. HIV-neg no-PrEP	0.19 [0.05–0.72] (0.0150)
Age>*35*	
HIV-neg PrEP vs. PLWHIV	3.54 [1.69–7.41] (0.0008)
HIV-neg No-PrEP vs. PLWHIV	3.13 [1.06–9.25] (0.0390)
HIV-neg PrEP vs. HIV-neg no-PrEP	1.13 [0.34–3.77] (0.8428)
	Rectal Site
HIV-neg PrEP vs. PLWHIV	1.12 [0.60–2.09] (0.7174)
HIV-neg no-PrEP vs. PLWHIV	1.38 [0.58–3.29] (0.4671)
HIV-neg PrEP vs. HIV-neg no-PrEP	0.81 [0.30–2.24] (0.6884)
PLWHIV *Age >35 vs. ≤35*	0.34 [0.17–0.67] (0.0018)
HIV-neg PrEP Age >35 vs. ≤35	3.04 [0.88–10.52] (0.0800)
HIV-neg no-PrEP Age >35 vs. ≤35	1.00 [0.21–4.70] (0.9960)
Age≤*35*	
HIV-neg PrEP vs. PLWHIV	0.21 [0.06–0.73] (0.0137)
HIV-neg no-PrEP vs. PLWHIV	0.61 [0.16–2.37] (0.4758)
HIV-neg PrEP vs. HIV-neg no-PrEP	0.35 [0.07–1.84] (0.2145)
Age>*35*	
HIV-neg PrEP vs. PLWHIV	1.92 [0.93–3.93] (0.0762)
HIV-neg no-PrEP vs. PLWHIV	1.80 [0.63–5.11] (0.2724)
HIV-neg PrEP vs. HIV-neg no-PrEP	1.07 [0.32–3.53] (0.9169)
	Pharyngeal Site
HIV-neg PrEP vs. PLWHIV	3.34 [1.46–7.66] (0.0044)
HIV-neg no-PrEP vs. PLWHIV	2.40 [0.62–9.36] (0.2075)
HIV-neg PrEP vs. HIV-neg no-PrEP	1.39 [0.33–5.89] (0.6536)
PLWHIV *Age >35 vs. ≤35*	0.17 [0.06–0.47] (0.0008)
HIV-neg PrEP Age >35 vs. ≤35	4.68 [0.93–23.50] (0.0610)
HIV-neg no-PrEP Age >35 vs. ≤35	1.09 [0.09–13.24] (0.9447)
Age≤*35*	
HIV-neg PrEP vs. PLWHIV	0.27 [0.05–1.44] (0.1242)
HIV-neg no-PrEP vs. PLWHIV	0.58 [0.06–5.20] (0.6237)
HIV-neg PrEP vs. HIV-neg no-PrEP	0.46 [0.04–6.00] (0.5557)
Age>*35*	
HIV-neg PrEP vs. PLWHIV	7.53 [2.92–19.45] (<0.0001)
HIV-neg no-PrEP vs. PLWHIV	3.80 [0.75–19.36] (0.1084)
HIV-neg PrEP vs. HIV-neg no-PrEP	1.98 [0.37–10.54] (0.4219)

[a] Adjusted for the number of visits.

3.3. Age and STI risk

Overall risk of STI did not appear to be significantly different according to age (>35 years vs. ≤35 years) in the unadjusted or the adjusted analysis for the number of screening visits (Table 2).

Overall age of more than 35 years seemed to be a risk factor for STIs in the group of PrEP users (OR 3.51 [1.37–8.99], p = 0.0091), while it acted rather as a "protective" factor in PLWHIV (OR 0.36 [0.20–0.65], p = 0.0007) (results not shown).

A finer analysis of the effect of age on STI risk showed that age >35 years was a lesser risk factor compared to age ≤35 years for chlamydia and rectal and pharyngeal STIs among PLWHIV (Tables 3 and 4). No effect for age group was observed for HIV-neg PrEP or No-PrEP users regarding the type or the site of STIs.

3.4. Longitudinal analysis of STIs risk

Longitudinal analysis allowed an approximative evolution of STI risk early after implementation of PrEP (first and second year), within, as well as between, the three risk groups of participants. The HIV-neg no-PrEP group remained at higher STI risk than PLWHIV and PrEP users during the two periods (Table 5). In the same way, while STI risk significantly increased during the second year for PLWHIV (OR 1.77 [1.23–2.55], p = 0.0020), it marginally increased for HIV-neg no-PrEP participants (OR 2.29 [0.91–5.73], p = 0.0774), and it remained rather stable for HIV-neg PrEP users (OR 1.19 [0.60–2.38], p = 0.6181).

3.5. Relationship between incident HIV/Hepatitis infections and STIs

Overall, we reported 10 cases of HIV seroconversion, all occurring within the HIV-neg no-PrEP group, 18 cases of HCV seroconversion (15 cases among PLWHIV and 3 cases among PrEP users) and 18 cases of HAV seroconversion (10 cases among PLWHIV, 4 cases among PrEP users, and 4 cases among no-PrEP users).

4. Discussion

To our knowledge, this is the first study to comparatively evaluate acquisition of STIs in different risk groups of MSM participants (PLWHIV, PrEP users, and HIV-neg no-PrEP users) in the current early era of HIV PrEP. Since PrEP approval, there is general concern that expanded use of PrEP may lead to increased incidence of bacterial STIs,[11–14] because of the true effect of behavioral disinhibition,[14–18] as well as the apparent effect of increased screening of persons involved in preventive healthcare. The overall rates of STIs in our study were lower than in other PrEP trials after adjustment for the number of screening visits, probably because of population differences.[19–24] Nevertheless, when compared to the Pre-exposure Prophylaxis Expanded (PrEPX) Study of the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS) clinic network,[19] we also observed that STIs were highly concentrated among a subset of persons that probably had more risky behavior.

We observed no statistically significant increase over time for HIV-neg PrEP-users, counter to HIV-neg no-PrEP users and PLWHIV, which might reflect the effect of close monitoring and counseling. It is crucial to notice that the comparative evaluation of STI incidence rates between HIV-neg PrEP and no-PrEP users rather suggests that it was not PrEP initiation per se that caused the observed global increase in STI risk.[19] STI incidence did not seem to increase in HIV-neg PrEP users during the second period of our study compared to the first.[25]

The number of HIV contaminations were all observed in the HIV-neg

Table 4
STI risks for the different sites of STIs.

Group	*Neisseria gonorrhoea*
	Multivariate[a] OR [95%CI] (p)
HIV-neg PrEP vs. PLWHIV	2.67 [1.45–4.91] (0.0016)
HIV-neg no-PrEP vs. PLWHIV	1.52 [0.53–4.37] (0.4349)
HIV-neg PrEP vs. HIV-neg no-PrEP	1.75 [0.56–5.46] (0.3326)
PLWHIV *Age >35 vs. ≤35*	0.58 [0.25–1.37] (0.2143)
HIV-neg PrEP Age >35 vs. ≤35	2.78 [0.92–8.36] (0.0689)
HIV-neg no-PrEP Age >35 vs. ≤35	0.51 [0.09–2.89] (0.4488)
Age≤*35*	
HIV-neg PrEP vs. PLWHIV	0.82 [0.25–2.72] (0.7446)
HIV-neg no-PrEP vs. PLWHIV	1.68 [0.39–7.29 (0.4886)
HIV-neg PrEP vs. HIV-neg no-PrEP	0.49 [0.10–2.37 (0.3730)
Age>*35*	
HIV-neg PrEP vs. PLWHIV	3.90 [1.92–7.92] (0.0002)
HIV-neg no-PrEP vs. PLWHIV	1.48 [0.41–5.38] (0.5560)
HIV-neg PrEP vs. HIV-neg no-PrEP	2.65 [0.66–10.61] (0.1695)
	Chlamydiae trachomatis
HIV-neg PrEP vs. PLWHIV	2.31 [1.16–4.58] (0.0167)
HIV-neg no-PrEP vs. PLWHIV	4.27 [1.70–10.73] (0.0020)
HIV-neg PrEP vs. HIV-neg no-PrEP	0.54 [0.19–1.54] (0.2482)
PLWHIV *Age >35 vs. ≤35*	0.25 [0.11–0.57] (0.0011)
HIV-neg PrEP Age >35 vs. ≤35	2.71 [0.77–9.59] (0.1226)
HIV-neg no-PrEP Age >35 vs. ≤35	0.41 [0.11–1.58] (0.1962)
Age≤*35*	
HIV-neg PrEP vs. PLWHIV	0.38 [0.10–1.38] (0.1403)
HIV-neg no-PrEP vs. PLWHIV	2.91 [0.87–9.68] (0.0824)
HIV-neg PrEP vs. HIV-neg no-PrEP	0.13 [0.03–0.59] (0.0081)
Age>*35*	
HIV-neg PrEP vs. PLWHIV	4.14 [1.86–9.21] (0.0005)
HIV-neg no-PrEP vs. PLWHIV	4.83 [1.58–14.83] (0.0059)
HIV-neg PrEP vs. HIV-neg no-PrEP	0.86 [0.25–2.96] (0.8057)
	Mycoplasma genitallium
HIV-neg PrEP vs. PLWHIV	1.23 [0.51–2.96] (0.6380)
HIV-neg no-PrEP vs. PLWHIV	2.44 [0.83–7.20] (0.1070)
HIV-neg PrEP vs. HIV-neg no-PrEP	0.51 [0.14–1.87] (0.3068)
PLWHIV *Age >35 vs. ≤35*	0.41 [0.15–1.11] (0.0802)
HIV-neg PrEP Age >35 vs. ≤35	0.80 [0.19–3.33] (0.7601)
HIV-neg no-PrEP Age >35 vs. ≤35	2.55 [0.26–24.66] (0.4198)
Age≤*35*	
HIV-neg PrEP vs. PLWHIV	0.75 [0.19–2.96] (0.6798)
HIV-neg no-PrEP vs. PLWHIV	0.62 [0.07–5.60] (0.6678)
HIV-neg PrEP vs. HIV-neg no-PrEP	1.21 [0.12–12.42] (0.8702)
Age>*35*	
HIV-neg PrEP vs. PLWHIV	1.45 [0.50–4.19] (0.4937)
HIV-neg no-PrEP vs. PLWHIV	3.79 [1.13–12.74] (0.0310)
HIV-neg PrEP vs. HIV-neg no-PrEP	0.38 [0.09–1.71] (0.2088)
	Treponema pallidum
HIV-neg PrEP vs. PLWHIV	0.96 [0.42–2.22] (0.9281)
HIV-neg no-PrEP vs. PLWHIV	2.70 [1.08–6.76] (0.0345)
HIV-neg PrEP vs. HIV-neg no-PrEP	0.36 [0.11–1.15] (0.0837)
PLWHIV *Age >35 vs. ≤35*	0.49 [0.20–1.22] (0.1259)
HIV-neg PrEP Age >35 vs. ≤35	2.21 [0.41–11.80] (0.3551)
HIV-neg no-PrEP Age >35 vs. ≤35	1.07 [0.23–4.98] (0.9302)
Age≤*35*	
HIV-neg PrEP vs. PLWHIV	0.31 [0.06–1.61] (0.1639)
HIV-neg no-PrEPnvs. PLWHIV	1.50 [0.34–6.54] (0.5906)
HIV-neg PrEP vs. HIV-neg No-PrEP	0.21 [0.03–1.44] (0.1110)
Age>*35*	
HIV-neg PrEP vs. PLWHIV	1.39 [0.53–3.64] (0.5070)
HIV-neg no-PrEP vs. PLWHIV	3.26 [1.10–9.66] (0.0333)
HIV-neg PrEP vs. HIV-neg no-PrEP	0.43 [0.11–1.66] (0.2178)

[a] Adjusted for the number of visits.

Table 5
Longitudinal analysis of STIs risk.

	Multivariate[a] OR [95%CI] (p)
Period 1	
HIV-neg *PrEP vs. PLWHIV*	1.80 [1.08–3.01] (0.0239)
HIV-neg no-PrEP vs. PLWHIV	3.10 [1.39–6.91] (0.0056)
HIV-neg PrEP vs. HIV-neg no-PrEP	0.58 [0.24–1.40] (0.2272)
Period 2	
HIV-neg *PrEP vs. PLWHIV*	1.21 [0.68–2.18] (0.5176)
HIV-neg no-PrEP vs. PLWHIV	4.00 [2.26–7.09] (<.0001)
HIV-neg PrEP vs. HIV-neg no-PrEP	0.30 [0.14–0.64] (0.0017)
PLWHIV P2 vs. P1	1.77 [1.23–2.55] (0.0020)
HIV-neg PrEP P2 vs. P1	1.19 [0.60–2.38] (0.6181)
HIV-neg no-PrEP P2 vs. P1	2.29 [0.91–5.73] (0.0774)

[a] Adjusted for the number of visits.

no-PrEP and incidence was slightly higher than in the IPERGAY study,[26] probably because of the real-life clinical setting.

In the limit of the retrospective nature of this study, our results suggest that efficient informing and follow-up of ambulatory MSM participants in the PrEP context would remain an important strategy for mitigating STI among those at risk, probably because of regular STI monitoring and prompt treatment. Even if the Achilles heel of PrEP has been medication adherence, it appears to be quite efficient in our real-life setting, because no HIV transmission was observed in the group of PrEP users. The apparent difference of STI incidence between PrEP and no-PrEP users would suggest that there is still need for progress, regarding access to PrEP and STI screening for a population that is currently more at risk for STIs and HIV than PrEP users. Our observations would support the need for larger availability of PrEP in MSM populations in Europe, as well as the need to test for infections not only upon clinical suspicion but as a routine sampling. Even if prospective long-term follow-up data are needed to confirm our observations, STI incidence should be closely monitored, especially regarding emergence of resistant bacteria, because the decreasing susceptibility of bacterial pathogens such as *Neisseria gonorrhoeae*[27–31] and *Mycoplasma genitalium*[32,33] to first-line antibiotic regimens is becoming a major health problem. Moreover, even if new and improved antiretrovirals (ARVs) are available to treat PLWHIV, they do not seem sufficient to fully address the HIV/AIDS epidemic without addressing behavioral health issues and improved access to evidence-based prevention interventions such as use of condoms, HIV PrEP, and male circumcision. This study suggests that a proactive approach—screening STIs in MSM with an efficient follow-up, and adequately informing ambulatory MSM participants after PrEP approval—may induce a significant decrease of STIs. These results imply that close monitoring and management can reduce STIs in MSM in the PrEP era.

5. Conclusions

PrEP is a proven effective strategy preventing HIV infection in different risk groups, but there is general concern that use of PrEP may lead to increased incidence of STI, especially in the context of ChemSex and substance use. Our results suggest that an efficient follow-up of MSM participants in the context of PrEP may have prevented an increase of the incidence of STIs among PrEP users.

Conflict of interest

Authors declare no association that might pose a conflict of interest.

Funding

None declared.

Ethical approval

Not required.

Contributions of authors

CKP, PH and PP designed the study. PP and MD were the trial physicians. PH and KCP coordinated the collection of medical data. HC coordinated serology tests and molecular biology analysis. GP did the analysis with advice from CKP, PH and PP. CKP prepared the original manuscript and contributed to subsequent revisions with advice from

PH, PP, FR and GP. All authors commented on the report and approved the final version.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to thank the study team and participants at the Department of Infectious Diseases and Internal Medicine of the European Hospital, Marseille.

References

1 CDC Media Relations. *New CDC Analysis Shows Steep and Sustained Increases in STDs in Recent Years*. Press Release; 2018. https://www.cdc.gov/media/releases/2018/p0828-increases-in-stds.html.
2 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;3:1386–1391.
3 CDC Media Relations. STDs in men who have sex with men. https://www.cdc.gov/std/stats16/msm.htm.
4 Pufall EL, Kall M, Shahmanesh M, et al. Sexualized drug use ('chemsex') and high-risk sexual behaviours in HIV-positive men who have sex with men. *HIV Med*. 2018;19:261–270.
5 Sewell J, Cambiano V, Miltz A, et al. Changes in recreational drug use, drug use associated with chemsex, and HIV-related behaviours, among HIV-negative men who have sex with men in London and Brighton, 2013-2016. *Sex Transm Infect*. 2018;94:494–501.
6 Drabo EF, Hay JW, Vardavas R, Wagner ZR, Sood N. A cost-effectiveness analysis of preexposure prophylaxis for the prevention of HIV among los angeles county men who have sex with men. *Clin Infect Dis*. 2016;63:1495–1504.
7 Stenger MR, Baral S, Stahlman S, Wohlfeiler D, Barton JE, Peterman T. As through a glass, darkly: the future of sexually transmissible infections among gay, bisexual and other men who have sex with men. *Sex Health*. 2017;14:18–27.
8 Newman L, Rowley J, Vander Hoorn S, et al. Global estimates of the prevalence and incidence of four curable sexually transmitted infections in 2012 based on systematic review and global reporting. *PLoS One*. 2015;10, e0143304.
9 Freeborn K, Portillo CJ. Does pre-exposure prophylaxis for HIV prevention in men who have sex with men change risk behaviour? A systematic review. *J Clin Nurs*. 2018;27:3254–3265.
10 Scott HM, Klausner JD. Sexually transmitted infections and pre-exposure prophylaxis: challenges and opportunities among men who have sex with men in the US. *AIDS Res Ther*. 2016;13:5.
11 Nguyen V-K, Greenwald ZR, Trottier H, et al. Incidence of sexually transmitted infections before and after preexposure prophylaxis for HIV. *AIDS*. 2018;32:523–530.
12 Lal L, Audsley J, Murphy DA, et al. Medication adherence, condom use and sexually transmitted infections in Australian preexposure prophylaxis users. *AIDS*. 2017;31:1709–1714.
13 Marcus JL, Hurley LB, Hare CB, et al. Preexposure prophylaxis for HIV prevention in a large integrated health care system: adherence, renal safety, and discontinuation. *J Acquir Immune Defic Syndr*. 2016;73:540–546.
14 Traeger MW, Schroeder SE, Wright EJ, et al. Effects of pre-exposure prophylaxis for the prevention of human immunodeficiency Virus infection on sexual risk behavior in men who have sex with men: a systematic review and meta-analysis. *Clin Infect Dis*. 2018;67:676–686.
15 Milam J, Jain S, Dubé MP, et al. Sexual risk compensation in a pre-exposure prophylaxis demonstration study among individuals at risk of HIV. *J Acquir Immune Defic Syndr*. 2019;80. e9–e13.
16 Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. 2010;363:2587–2599.
17 Newcomb ME, Moran K, Feinstein BA, Forscher E, Mustanski B. Pre-exposure prophylaxis (PrEP) use and condomless anal sex: evidence of risk compensation in a cohort of young men who have sex with men. *J Acquir Immune Defic Syndr*. 2018;77:358–364.
18 Hoornenborg E, Coyer L, van Laarhoven A, et al. Change in sexual risk behaviour after 6 months of pre-exposure prophylaxis use: results from the Amsterdam pre-exposure prophylaxis demonstration project. *AIDS*. 2018;32:1527–1532.
19 Traeger MW, Cornelisse VJ, Asselin J, et al. Association of HIV preexposure prophylaxis with incidence of sexually transmitted infections among individuals at high risk of HIV infection. *JAMA*. 2019;321:1380–1390.
20 McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet*. 2016;387:53–60.
21 Volk JE, Marcus JL, Phengrasamy T, et al. No new HIV infections with increasing use of HIV preexposure prophylaxis in a clinical practice setting. *Clin Infect Dis*. 2015;61:1601–1603.
22 Liu AY, Cohen SE, Vittinghoff E, et al. Preexposure prophylaxis for HIV infection integrated with municipal- and community-based sexual health services. *JAMA Intern Med*. 2016;176:75–84.
23 Hare CB, Coll J, Ruane PJ, et al. The phase 3 DISCOVER study: daily F/TAF or F/TDF for HIV preexposure prophylaxis. In: *Conference on Retroviruses and Opportunistic Infections (CROI)*. Washington: Seattle; March 4–7, 2019. Abstract 104.
24 Jenness SM, Weiss KM, Goodreau SM, et al. Incidence of gonorrhea and Chlamydia following human immunodeficiency Virus preexposure prophylaxis Among men who have sex with men: a modeling study. *Clin Infect Dis*. 2017;65:712–718.
25 Hosek SG, Rudy B, Landovitz R, et al. An HIV preexposure prophylaxis demonstration project and safety study for young MSM. *J Acquir Immune Defic Syndr*. 2017;74:21–29.
26 Pillet M, Cua E, Capitant C, et al. Risk factors for HIV infection among MSM in the ANRS IPERGAY PrEP trial. In: *Conference on Retroviruses and Opportunistic Infections (CROI)*. Washington: Seattle; March 4–7, 2019. Abstract 846.
27 Cole MJ, Spiteri G, Jacobsson S, et al. Overall low extended-spectrum cephalosporin resistance but high azithromycin resistance in Neisseria gonorrhoeae in 24 European countries, 2015. *BMC Infect Dis*. 2017;17:617.
28 Eyre DW, Town K, Street T, et al. Detection in the United Kingdom of the Neisseria gonorrhoeae FC428 clone, with ceftriaxone resistance and intermediate resistance to azithromycin, October to December 2018. *Euro Surveill*. 2019;24.
29 Chisholm SA, Wilson J, Alexander S, et al. An outbreak of high-level azithromycin resistant Neisseria gonorrhoeae in England. *Sex Transm Infect*. 2016;92:365–367.
30 Harris SR, Cole MJ, Spiteri G, et al. Public health surveillance of multidrug-resistant clones of Neisseria gonorrhoeae in Europe: a genomic survey. *Lancet Infect Dis*. 2018;18:758–768.
31 Tacconelli E, Pezzani MD. Public health burden of antimicrobial resistance in Europe. *Lancet Infect Dis*. 2019;19:4–6.
32 Couldwell DL, Jalocon D, Power M, Jeoffreys NJ, Chen SC-A, Lewis DA. Mycoplasma genitalium: high prevalence of resistance to macrolides and frequent anorectal infection in men who have sex with men in western Sydney. *Sex Transm Infect*. 2018;94:406–410.
33 Allan-Blitz L-T, Mokany E, Campeau S, Wee R, Shannon C, Klausner JD. Prevalence of mycoplasma genitalium and azithromycin-resistant infections among remnant clinical specimens, los angeles. *Sex Transm Dis*. 2018;45:632–635.