



BMJ Open Characteristics of HIV pre-exposure prophylaxis users at first PrEP counselling visit: the CSL-PrEP cohort

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ABSTRACT

Objectives Pre-exposure prophylaxis (PrEP) is effective for HIV prevention and is mostly used by men who have sex with men (MSM). The aim of this study was to describe the characteristics of a cohort of PrEP users at first PrEP counselling visits (baseline, BL).

Design Cross-sectional study of a cohort of MSM receiving PrEP (Centro San Luigi, CSL-PrEP Cohort).

Setting Secondary-level sexually transmitted infections (STI) centre in Milan, Italy, from May 2017 to May 2022.

Participants Overall, 624 MSM PrEP users were included; most users were Caucasian (97%), attended university (64%), with a median BL age of 34.5 years.

Results Overall, 45% choose the daily-based PrEP regimen, 55% the event-based one. An increasing trend in PrEP counselling visits was observed ($p=0.024$). The majority had between 10 and 19 partners in the 3 months before BL and 41% were chemsex users. All had a HIV Incidence Risk Index for MSM (HIRI-MSM) >10 , 54% between 20 and 29. Overall, 50% had ≥ 1 previous STI and 22% ≥ 1 BL STI. BL chlamydia (10%) was often more frequent than in the past (7%). The number of sexual partners was associated with BL chlamydia ($p<0.001$), gonorrhoea ($p=0.002$) and syphilis ($p<0.001$), HIRI-MSM with chlamydia ($p=0.001$) and gonorrhoea ($p=0.008$), chemsex use with chlamydia ($p=0.003$) and gonorrhoea ($p=0.030$).

Conclusions We observed an unbalanced access to PrEP in respect to all key populations which might benefit from PrEP, with a similar choice for event-based or daily-based regimens. High-risk behaviours and STIs were frequently observed. History of chlamydia was very frequently high in asymptomatic MSM at BL, compared with what observed before access to PrEP. High-risk behaviours and HIRI-MSM were associated with most of STIs.

INTRODUCTION

Although the incidence of HIV has been declining over the past 10 years, 104.765 new HIV diagnoses (incidence 15.6:100 000) were made in 2020 in the WHO European Region, with 39% of infections occurring among men who have sex with men (MSM).¹ Focusing on Italy, the number of HIV infections has been

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Individuals attending our centre for pre-exposure prophylaxis (PrEP) are followed in a dedicated clinic, with detailed investigations on risk factors, previous and current sexually transmitted infections, PrEP regimen choice, laboratory, serologic and virologic data; this process may guarantee the acquisition of complete data on PrEP users recorded into the Centro San Luigi (CSL)-PrEP cohort.
- ⇒ This is a monocentric, cross-sectional study on a single cohort of people with no control group.
- ⇒ The type of PrEP-regimen chosen at baseline might have changed over time; changes over time will be recorded and evaluated in future studies.
- ⇒ The cohort includes cisgender-men who have sex with men only and no other key population who might benefit from PrEP access.

decreasing stably since 2012, with an incidence of 4.2:100 000 in 2019. Overall, almost half of HIV infections occurred among MSM in 2019 in Italy, which was higher than in Europe. The number of new HIV diagnoses among foreigners has been decreasing since 2016. In spite of the preventive efforts adapted nationally, the number of late presenters has been increasing since 2017, with a stable number of AIDS-related deaths. The city of Milan was one of those with the highest HIV incidence in Italy and with the highest number of HIV diagnoses among MSM.² This highlights the ongoing need for new and effective preventive strategies. HIV pre-exposure prophylaxis (PrEP) is an effective form of HIV infection prevention, which is based on oral antiretrovirals that should be taken before sexual exposure.³ Moreover, PrEP completes the arsenal of HIV preventive strategies already available such as treatment as prevention, postexposure prophylaxis and safe sexual practices.⁴ In Europe, only the PrEP formulation based on

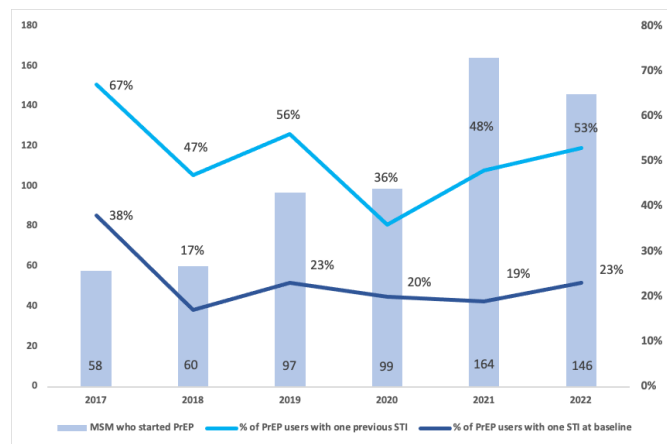


Figure 1 PrEP beginning and STIs diagnosis over years. MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection.

oral emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) is licensed and two regimens are approved: daily-based (one pill every day) and event-based (two pills prior to exposure, one pill after 24 hours and 48 hours).⁵ Most PrEP users in Europe, Italy and Milan belong to key populations, such as MSM and sex workers.^{3 6–9} PrEP is available in Italy since 2017, on prescription from an infectious diseases specialist. Though, to date, it is not reimbursed through the National Health Service; individuals have to buy generic formulations of FTC/TDF out-of-pocket. Regarding the sexually transmitted infections (STIs), screenings should be conducted at PrEP prescription and during follow-up, there are several regional differences in Italy, but most PrEP centres can provide both HIV and STI screening free of charge. In a recent survey, it has been estimated that almost 70 centres currently prescribe PrEP in Italy and 7 of them are based in Milan. The only available multicentre data, estimated that more than 3,500 individuals receive PrEP prescription in Italy and 95% of them is an MSM; though, these data are likely underestimated.⁸ Moreover, in other cohorts of PrEP users in Milan, frequent presence of high-risk sexual behaviours was described.^{9 10} Among individuals accessing PrEP, high-risk sexual behaviours are very common; for instance, the sexualised use of chems (chemsex), which is associated with an higher risk of HIV and STIs acquisition, is frequent among PrEP users.^{11–13} Moreover, STI diagnoses are common, especially referring to bacterial ones, including gonorrhoea, chlamydia and syphilis.^{2 7 14} PrEP counselling might be an opportunity not only to offer an effective form of HIV prevention but also to expand accessibility to STI screening among asymptomatic MSM who report high-risk sexual behaviours.

The aims of this study were to describe PrEP users' characteristics at their first PrEP counselling visit (baseline, BL), to evaluate the prevalence of high-risk behaviours, to assess STIs clinical history and BL STIs prevalence and to evaluate the association of high-risk behaviours with BL STIs.

METHODS

This is a cross-sectional study of a cohort of MSM receiving PrEP at the Infectious Diseases Unit of IRCCS San Raffaele, Milan. All individuals who received PrEP counselling and prescription visit from May 2017 (first PrEP visit conducted at our centre) to May 2022 (freezing date) were included in the study. Individuals receiving PrEP at the Infectious Diseases Unit of IRCCS San Raffaele, Milan are followed in a dedicated clinic, with free of charge HIV and STI testing and access to STI vaccines. Informed consent for inclusion in the study and for publication was obtained from all individuals included in the study out of all those who received PrEP prescription at the Infectious Diseases Unit of IRCCS San Raffaele, Milan. Data from individuals who did not provide informed consent were not included in this study. Anonymised data were collected by means of the electronic health records of all PrEP users (Centro San Luigi (CSL) CSL-PrEP Cohort), which includes demographic data, risk factors, clinical history, PrEP regimen choice, laboratory, serologic and virologic data. The BL PrEP regimen choice referred to the future intended use. High-risk behaviours were collected by means of a validated questionnaire self-completed at BL, including the number of partners, chemsex use and previous STIs and date of diagnosis (HIV Incidence Risk Index for MSM, HIRI-MSM).¹⁵ Considered previous STIs refer to all available previous medical history, for HIRI-MSM to the 3 months prior to BL visit. The HIRI-MSM is a 7-item screening index that is predictive of HIV seroconversion among MSM, which was adopted in Italian HIV guidelines for prioritisation of PrEP prescription.⁷ Individuals accessing the Infectious Diseases Unit of IRCCS San Raffaele, Milan were offered PrEP according to international and Italian PrEP guidelines, which recommend offering PrEP to all individuals who are at high risk of contracting HIV, evaluated by the assessment of HIRI-MSM, which should be superior than 10.¹⁶ At BL, following counselling, HIV and STI testings were performed and serum creatinine and transaminase levels dosed, as recommend by Italian and international PrEP guidelines.^{16 17} Included STIs were syphilis (Gralis 2000 Boute), gonorrhoea (gonococcal specific cultures or Cobas 6800 Roche nucleic acid amplification test, NAAT) and chlamydia (Cobas 6800 Roche NAAT) at urethral, rectal and pharyngeal sites. No individual had STI symptoms at BL.

The median (quartile 1, quartile 3) and the frequency (%) were used, as appropriate, to describe the individuals' characteristics; comparisons between daily-based and event-based PrEP regimens were performed by use of the χ^2 /Fisher's exact test or the Mann-Whitney test for the categorical and the continuous variables, respectively.

Comparison of paired proportions was performed using McNemar test.

Trend in the number of first PrEP counselling visits over time was tested by Mann-Kendall trend test. Cochran-Armitage test was used to assess linear trend in STI prevalence over time and linear trend in daily-based and

Table 1 Individuals' characteristics at BL by PrEP regimen

Characteristics	Overall (n=624)	Event-based (n=344)	Daily-based (n=280)	P value
BL age (years; median (IQR))*	34.5 (30.1; 40.2)	34.2 (30.6; 39.7)	34.8 (29.8; 41.2)	0.665
Ethnicity††				0.09
Caucasian	606 (97.1%)	338 (98.3%)	268 (95.7%)	
Non-Caucasian	18 (2.9%)	6 (1.7%)	10 (3.6%)	
Chemsex‡§†	258 (41.3%)	137 (39.8%)	121 (43.2%)	0.439
Number of sexual partners†§				0.221
0–9	261 (41.8%)	143 (41.6%)	118 (42.1%)	
10–19	204 (32.7%)	121 (35.2%)	83 (29.6%)	
20–49	125 (20.0%)	66 (19.2%)	59 (21.1%)	
>50	34 (5.45%)	14 (4.07%)	20 (7.14%)	
Previous STI**†	313 (50.2%)	165 (48.0%)	148 (52.9%)	0.256
HIRI-MSM†	67 (10.7%)	35 (10.2%)		0.881
10–19	337 (54.0%)	187 (54.4%)	32 (11.4%)	
20–29	220 (35.3%)	122 (35.5%)	150 (53.6%)	
>30			98 (35.0%)	
Education†				0.993
Middle school	13 (2.08%)	7 (2.03%)	6 (2.14%)	
Upper school	215 (34.5%)	119 (34.6%)	96 (34.3%)	
University	396 (63.5%)	218 (63.4%)	178 (63.6%)	
Year of BL visit†				<0.001
2017	58 (9.29%)	3 (0.87%)	55 (19.6%)	
2018	60 (9.62%)	20 (5.81%)	40 (14.3%)	
2019	97 (15.5%)	40 (11.6%)	57 (20.4%)	
2020	99 (15.9%)	57 (16.6%)	42 (15.0%)	
2021	164 (26.3%)	111 (32.3%)	53 (18.9%)	
2022	146 (23.4%)	113 (32.8%)	33 (11.8%)	

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*Mann-Whitney test

†Chi-square/Fisher's exact test.

‡Non-Caucasian category included eight *Hispanic/Latino people*, eight *Black/African-American people* and two *Asian people*.

§Referred to the 3 months prior to BL visit.

¶Sexualised use of either cocaine (hydrochloride or freebase), mephedrone, gamma hydroxybutyrate (GHB), gamma butyrolactone (GBL), crystal methamphetamine, ketamine or methylenedioxypyrovalerone (MDPV).

**Referred to all previous medical history.

BL, baseline; HIRI-MSM, HIV Incidence Risk Index for MSM; MSM, men who have sex with men; STI, sexually transmitted infection.

event-based PrEP regimens' choice. Associations between the number of partners in the previous 3 months, HIRI-MSM and chemsex with presence of STIs at BL were assessed by χ^2 /Fisher's exact test. A two-sided probability value (p value) < 0.05 was considered statistically significant. All the analyses were done using SAS, V.9.4 (SAS Institute, Cary, North Carolina).

Patient and public involvement statement

The design of the study and the implementation of the CSL-PrEP were made also with the help of individuals accessing PrEP. Moreover, people living with HIV (PLWH) in care at our centre were informed about the CSL-PrEP Cohort and its purpose. Moreover, both individuals

accessing PrEP and PLWH were central to the dissemination of the BL information, which helped to motivate community involvement during and beyond the study.

RESULTS

Individuals' characteristics

Overall, 624 out of 642 (97%) individuals receiving PrEP at the Infectious Diseases Unit of IRCCS San Raffaele were included in the study: 100% were cisgender-MSM, 280 (44.9%) were taking the daily-based PrEP regimen and 344 (55.1%) the event-based one.



Figure 2 Trends of previous and BL STIs over years: (A) chlamydia, (B) gonorrhoea and (C) syphilis. BL, baseline; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection.

An increasing trend in the number of first PrEP counselling visits was observed over years ($p=0.024$) (figure 1).

Individuals' characteristics according to the PrEP regimen choice are presented in table 1: most PrEP users were Caucasian (606, 97%) and attended university (396, 64%), with a median age at BL of 34.5 (IQR 30.1–40.2).

Overall, the majority had between 10 and 19 partners in the 3 months before PrEP counselling visits and 41% reported engagement in the sexualised use of chems. All individuals had a HIRI-MSM higher than 10 and the majority between 20 and 29 (337/624, 54%). Among all individuals, five were sex workers: all had >50 partners in the previous 3 months, were chemsex users, had a HIRI-MSM >30 and choose the daily-based PrEP regimen.

When comparing individuals choosing event-based or daily-based PrEP, more Caucasians chose event-based PrEP (338/344, 98.3% vs 268/280, 95.7%, $p<0.001$), whereas more non-Caucasians chose daily-based PrEP (12/280, 4.3% vs 6/344, 1.7%, $p<0.001$). Moreover, we observed differences between the chosen regimen in relation to the year of BL visit ($p<0.001$), with an increasing trend of choice of the event-based regimen over years. No other significant differences were detected between individuals choosing event-based or daily-based PrEP, for instance, regarding age at BL (event based: 34.2 (IQR 30.6–39.7); daily based: 34.8 (IQR 29.8–41.2), $p=0.665$) or chemsex use (event based: 137, 40%; daily based: 121, 43%, $p=0.439$).

Median BL aspartate transaminase (U/L: 28, IQR 23–33), alanine transaminase (U/L: 27, IQR 21–36) and creatinine (mg/dL: 1.00, IQR 0.92–1.08) levels were all within normal ranges, allowing PrEP prescription.

Sexually transmitted infections

Overall, 313 (50%) MSM had ≥ 1 previous STI and 138 (22%) ≥ 1 STI at BL.

Trends of having received ≥ 1 past STI diagnosis and having ≥ 1 BL STI remained stable over time (BL STIs: $p=0.126$; previous STIs: $p=0.184$) (figure 1).

Bacterial STIs were more frequent than viral STIs: chlamydia was the STI more frequently detected at BL, whereas syphilis was the most frequent one in past history.

BL chlamydia ($n=64$) was often more frequent than in the past ($n=46$), trends of BL and previous chlamydia remained stable over time (BL: $p=0.721$; previous: $p=0.833$) (figure 2a). BL rectal chlamydia ($n=59$, 9.5%) was more frequent than in the past ($n=22$, 3.5%); BL urethral were 25 (4.0%), previous ones were 6 (1.0%).

BL gonorrhoea ($n=45$) was less frequent than in the past ($n=131$), trends of BL and previous gonorrhoea remained stable over time (BL: $p=0.401$; previous: $p=0.235$) (figure 2b). BL rectal gonorrhoea were 34 (5.4%), previous ones were 32 (5.1%); BL urethral were 11 (1.8%), previous ones were 98 (15.7%).

BL syphilis ($n=29$, 4.6%) was less frequent than in the past ($n=154$, 24.7%), trends of BL syphilis remained stable over time, trends of previous ones reduced (BL: $p=0.284$; previous: $p=0.011$) (figure 2c).

Among viral STIs, we detected only four cases of hepatitis C virus at BL and two previous ones; we did not detect any hepatitis B virus at BL.

Comparison of paired proportions of previous revealed differences regarding syphilis ($p<0.001$), gonorrhoea at any site ($p<0.001$) and chlamydia at the urethral ($p=0.001$) and rectal site only ($p<0.001$) between previous and BL diagnoses.

Full detail of previous and BL STIs is presented in table 2.

Association of high-risk behaviours and BL STIs

The number of sexual partners (0–9 vs 10–19 vs 20–49 vs >50) was associated with BL chlamydia (10/261, 3.8% vs

Table 2 Previous and BL STIs

Characteristics	Previous: No; Baseline: No	Previous: Yes; Baseline: No	Previous: No; Baseline: Yes	Previous: Yes; Baseline: Yes	P value*
Bacterial STIs					
Syphilis	453 (72.6%)	142 (22.8%)	17 (2.7%)	12 (1.9%)	<0.001
Chlamydia	517 (82.9%)	43 (6.9%)	61 (9.8%)	3 (0.5%)	0.095
Rectal	545 (87.3%)	20 (3.2%)	57 (9.1%)	2 (0.3%)	
Pharyngeal	622 (99.7%)	1 (0.2%)	1 (0.2%)	0 (0%)	
Uethral	593 (95.0%)	25 (4.0%)	6 (1.0%)	0 (0%)	
Gonorrhoea	462 (74%)	117 (18.7%)	31 (5.0%)	14 (2.2%)	<0.001
Rectal	563 (90.2%)	27 (4.3%)	29 (4.6%)	5 (0.8%)	
Pharyngeal	611 (98.0%)	8 (1.3%)	5 (0.8%)	0 (0%)	
Urethral	518 (83.0%)	95 (15.2%)	8 (1.3%)	3 (0.5%)	
Viral STIs					
HPV	564 (90.3%)	59 (9.4%)	1 (0.2%)	0 (0%)	<0.001
Viral hepatitis					
HAV	581 (93.0%)	42 (6.7%)	1 (0.2%)	0 (0%)	<0.001
HBV	613 (98.2%)	11 (1.8%)	0 (0%)	0 (0%)	–
HCV	618 (99.0%)	2 (0.3%)	4 (0.6%)	0 (0%)	0.683
HSV	607 (97.2%)	17 (2.7%)	0 (0%)	0 (0%)	–

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*McNemar test.

STI, sexually transmitted infection; HPV, human papilloma virus; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus.

11/204, 5.4% vs 34/125, 27.2% vs 9/34, 26.5%, $p<0.001$), BL gonorrhoea (9/261, 3.4% vs 16/204, 7.8% vs 14/125, 11.2% vs 6/34, 17.6%, $p=0.002$) and BL syphilis (4/261, 1.5% vs 8/204, 3.9% vs 13/125, 10.4% vs 4/34, 11.8%, $p\leq 0.001$). HIRI-MSM (10–19 vs 20–29 vs >30) was associated with BL chlamydia (0/67, 0% vs 34/337, 10.1% vs 30/220, 13.6%, $p=0.001$) and BL gonorrhoea (0/67, 0% vs 23/337, 6.8% vs 22/220, 10%, $p=0.008$), but not with BL syphilis (1/67, 1.5% vs 14/337, 4.2% vs 14/220, 6.4%, $p=0.250$). Being a chemsex user was associated with BL chlamydia (38/258, 14.7% vs 26/366, 7.1%, $p=0.003$) and BL gonorrhoea (26/258, 10.1% vs 19/366, 5.2%, $p=0.030$), but not with BL syphilis (16/258, 6.2% vs 13/366, 3.6%, $p=0.175$).

CONCLUSIONS

In Europe, Italy and Milan, there is still an ‘unbalanced’ access to PrEP when compared with all key populations who might theoretically benefit from PrEP: for instance, it has been estimated that around 500 million MSM in Europe cannot access PrEP despite being very likely to use it (‘PrEP gap’).¹⁸ In Italy, access to PrEP can be considered less challenging, depending on regional variabilities, as often the HIV and STI screenings required for PrEP prescription and during follow-up are free of charge; though, being PrEP not reimbursed by the National Health Service, access to PrEP might be particularly challenging for the youngest.^{8 19} All in all, currently, there is still a lack of access to PrEP in Italy; in fact, findings from our cohort showed that most PrEP users were high educated, Caucasian adults, without inclusion of transgender individuals and few foreigners. HIV prevention should aim to target

all key populations, therefore, including not only MSM coming from different backgrounds, such as the youngest and foreigners, but also women and transgender individuals. In our cohort, all individuals were cisgender-MSM, with no cisgender-women, transgender-women or transgender-men. Reassuringly, we observed a significant rising trend in the number of PrEP counselling visits conducted at our centre and no boundaries in PrEP prescription imposed by out of range renal or hepatic blood values, which suggest that, over time, access to PrEP is becoming easier, also thanks to community empowerment.¹⁹

Event-based and daily-based PrEP regimens have demonstrated to have similar efficacy rates in preventing HIV infection.² Individuals choose the regimen mostly depending on the characteristics of their sexual behaviours. We observed similar proportions of people choosing for event-based or daily-based PrEP use in our cohort, without significant differences with regards to age, the number of sexual partners and HIRI-MSM. Although having a high number of sexual partners should lead to the choice of daily PrEP, it is possible that individuals who have a high number of partners in a reduced time-frame, such as weekends, might opt for the event-based regimen. On the opposite, all individuals with a high number of partners who were sex workers opted for the daily-based regimen. Moreover, we observed a significant rising trend in the choice of event-based regimen over years, which could be linked to the increased access to PrEP in our cohort. The possibility of PrEP prescription also to individuals who are interested in HIV prevention but have less urgency to receive this preventive method when compared with those who started PrEP several years

ago might have led to the observed shift in PrEP regimen choice. Possibly, the SARS-CoV-2 pandemic might have influenced the sexual behaviours of the individuals accessing PrEP and, as a consequence, might explain the increasing trend of the choice of the event-based regimen.^{20 21} Though, our PrEP clinic was closed only for less than 2 months (March–April 2020), in which remote counselling was always available. We did not observe a significant difference in the regimens' choice among chemsex users.

In our cohort, we frequently observed high-risk behaviours, such as having a high number of partners and a broad diffusion of chemsex use, as corroborated by the high values of HIRI-MSM observed. Previous STIs were reported by half of the individuals, although having received one STI diagnosis was not required for prescribing PrEP in accordance with Italian guidelines, as HIRI-MSM >10 was observed among all individuals. The most frequent previous STIs were syphilis, possibly due to the relative easiness of serologic testing, followed by gonorrhoea, especially at urethral sites, being more often symptomatic. BL STIs were detected in almost a quarter of individuals. Furthermore, history of chlamydia was found to be very frequently high in asymptomatic MSM at PrEP counselling visit, compared with what observed before access to PrEP. As chlamydia often is asymptomatic, this might possibly suggest that, in our cohort, most individuals did not receive adequate STI screenings prior to the PrEP counselling visit.

We detected an association between the number of partners, chemsex use and HIRI-MSM with most of STIs, corroborating the idea that these parameters should be used as indicators for HIV/STIs risk and should be assessed during PrEP counselling to correctly evaluate the possible preventive strategies.

The results of this study are in line with other European cohorts, confirming that among PrEP users, high-risk sexual behaviours are very common; though, we found a significantly high number of PrEP users who reported chemsex use when compared with other studies.^{3 6 7 9 22 23}

We acknowledge that this is a cross-sectional study, with no control group as reference. The considered PrEP-regimen choice at BL, which refers to the planned future use, might have changed over time; changes over time will be recorded and evaluated in future studies. Moreover, not all individuals who accessed PrEP at our clinic provided consent for inclusion in the CSL-PrEP Cohort. However, being this number little when compared with the included individuals, we believe that the results of this study well represent PrEP users. As, our centre is just one of the hospital-based or community-based settings in Milan or Italy which provides PrEP, the results of this study might not be generalised to the whole country. In fact, we cannot exclude that there are differences between individuals accessing different centres which provide PrEP, though we believe that in the area of Milan this is not the case. Finally, we acknowledge that our results apply to the context of cisgender-MSM only, as no cisgender-women,

transgender-women or transgender-men were included in the study.

Our large cohort of PrEP users was mostly made of high-educated, Caucasian adults, who frequently reported high-risk sexual behaviours and prior STIs. At first PrEP counselling visit, STIs were frequently detected and we observed a similar preference for the daily-based or the event-based PrEP regimens although the event-based choice increased over time. Moreover, the number of partners, chemsex use and HIRI-MSM were associated with most BL STIs.

Contributors All authors contributed to the study conception and design and approved the final version of the article. SN conceived the study, performed medical visits and contributed to the writing of the article. ARR performed medical visits, collected clinical data and contributed to the writing of the article. RL collected clinical data and contributed to the reviewing of the article. DC and LG performed statistical analyses and contributed to the writing of the article. FA collected clinical data and contributed to the reviewing of the article. EB and DC contributed to the revision of literature and the writing of the article. MS, MR and CB contributed to the reviewing of the article. AC coordinated clinical activities and contributed to the reviewing of the article. SN is the guarantor of this article.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Consent obtained directly from patient(s)

Ethics approval The CSL Cohort was approved by the ethics committee of the San Raffaele Hospital, Milan, Italy (date of approval: 4 December 2017, protocol n. 34); on their first visit, individuals provide written informed consent on the use of their data in scientific analyses. Recorded data were anonymised and managed according to the Good Clinical Practice. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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