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ORIGINAL ARTICLE

Incidence of sexually transmitted infections and association with behavioural factors: Time-to-event analysis of a large pre-exposure prophylaxis (PrEP) cohort

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Abstract

Objectives: Our objective was to obtain long-term data on the incidence of sexually transmitted infections (STIs) and their association with behavioural factors after widespread pre-exposure prophylaxis (PrEP) implementation.

Methods: This was a time-to-event analysis of a national PrEP cohort in Switzerland (SwissPrEPared study). Participants were people without HIV interested in taking PrEP with at least two STI screening visits. Primary outcomes were incidence rate of gonorrhoea, chlamydia, and syphilis. The association between behavioural factors and STI diagnosis was expressed using hazard ratios. We adjusted for testing frequency and calendar year.

Results: This analysis included 3907 participants enrolled between April 2019 and April 2022, yielding 3815.7 person-years of follow-up for gonorrhoea (15 134 screenings), 3802.5 for chlamydia (15 141 screenings), and 3858.6 for syphilis (15 001 screenings). The median age was 39 years (interquartile range [IQR] 32–47), 93.8% ($n = 3664$) identified as men who have sex with men (MSM). The incidence was 22.8 (95% confidence interval [CI] 21.3–24.4) per 100 person-years for gonorrhoea, 26.3 (95% CI 24.7–28.0) for chlamydia, and 4.4 (95% CI 3.8–5.1) for syphilis. Yearly incidence rates decreased between 2019 (all bacterial STIs: 81.6; 95% CI 59.1–109.9) and 2022 (all bacterial STIs: 49.8; 95% CI 44.6–55.3). Participants reporting chemsex substance use were at higher risk of incident STIs, as were those reporting multiple sexual partners. Younger age was associated with a higher risk of gonorrhoea and chlamydia.

Conclusions: Incidence rates of bacterial STIs decreased over time. Young MSM, those with multiple partners, and those using chemsex substances were at increased risk of STIs.

KEYWORDS
behavioural factors, incidence rate, pre-exposure prophylaxis, sexually transmitted infections

INTRODUCTION

Pre-exposure prophylaxis (PrEP) has become a central element of HIV prevention since the first trials showed high efficacy in men who have sex with men (MSM) [1–3]. As of 2020, 180 countries have adopted the World Health Organization (WHO) recommendations on PrEP, with a global projected number of PrEP users of nearly 3 million by the end of 2023 [4]. In Switzerland, a large part of PrEP implementation is achieved through the SwissPrEPared programme, a national prevention programme launched in April 2019 [5], which provides PrEP counselling and regular medical assessments.

With the rapid development of PrEP programmes and wide uptake of PrEP in communities at considerable risk of HIV, several studies have reported a decline in incident HIV infections at a population level [6–12]. However, concern remains that PrEP may contribute to the current resurgence of other sexually transmitted infections (STIs), such as gonorrhoea, chlamydia, and syphilis [13–15], although this increase in STIs pre-dated the introduction of PrEP [16]. Among other factors, PrEP use

has been associated with changes in sexual behaviour, such as a decrease in condom use [17–20], but these findings have been inconsistent [21, 22]. In addition, there is considerable uncertainty as to how STI incidence rates evolve in the specific context of PrEP programmes, since frequent testing of people at considerable risk of infection may improve STI control ('test and treat' strategy) and reduce the overall incidence of STIs [15, 23–25]. Therefore, the objectives of this study were to determine the incidence of gonorrhoea, chlamydia, and syphilis in the ongoing SwissPrEPared cohort over a 3-year period and to evaluate the association between STI diagnosis and behavioural factors such as condom use, number of partners, and substance use in a sexual context.

MATERIALS AND METHODS

Patient consent statement

We followed the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) statement for the reporting of observational studies [26]. The SwissPrEPared study was approved by all local ethical committees (lead committee: Zurich, Switzerland—registration number: 2018–02015) and was registered with ClinicalTrials.gov (NCT03893188). Written informed consent was obtained from all participants.

Study design and setting

Data were extracted from the ongoing SwissPrEPared study, which is a national, multicentre cohort following individuals interested in taking PrEP to prevent HIV infection. The study design and cohort profile have been described elsewhere [5]. In brief, recruiting centres are located in 12 of 26 federal states (i.e., cantons) of Switzerland, which include tertiary and cantonal hospitals, community-based, voluntary counselling and testing services ("Checkpoints"), and private medical practices (e.g., general practitioners, infectious diseases specialists or dermatologists).

All participating centres are part of the SwissPrEPared programme, which ensures standardization of PrEP counselling across Switzerland. Programme participants complete standardized, smartphone-compatible questionnaires accessed through a secured, web-based, online platform before their scheduled visit. Visits consist of PrEP counselling and a medical assessment (including STI screening); these occur at regular intervals, i.e., every 3 months for participants on daily PrEP and at least every 6 months for those taking PrEP intermittently (i.e., either daily for limited periods of time ["holiday PrEP"] or before and after sex ["event-driven" PrEP]) [3].

Study participants

Potential study participants considered at considerable risk of HIV are informed about the possibility of study enrolment in print and online magazines and through outreach workers at specific events for MSM and trans people. The SwissPrEPared cohort includes people without HIV presenting for PrEP counselling at participating centres. Although the cohort mostly includes individuals on PrEP, those with no current recommendation for PrEP or those declining further PrEP use are not actively excluded, provided they plan to attend at least one follow-up visit (e.g. for STI screening or revaluation of PrEP need). For this analysis, only participants with at least two visits for STI testing were included.

Study outcomes

The primary outcome was the incidence of STIs, i.e., a new diagnosis of gonorrhoea, chlamydia, or syphilis (see Data S1 Methods 1 for a description of the laboratory tests). For syphilis, we considered primary, secondary, tertiary (defined as "active"), and latent infections. We also determined STI prevalence at study start. Screening was performed at each follow-up visit, irrespective of the presence or absence of symptoms.

We explored the association of STI diagnosis with the following behavioural factors: smoking (binary variable), number of partners (steady and casual, since last visit, categorized into 0–2, 3–10, >10), frequency of condom use with casual partners (categories: never, sometimes, mostly, always), and chemsex substance use (defined as the use of methamphetamine, mephedrone or gamma hydroxybutyrate [GHB]/gamma-butyrolactone [GBL] in a sexual context). The recall period for behavioural variables was 3 months unless otherwise specified.

Statistical methods

This analysis included data collected over a period of 3 years, starting from study inception. We expected fewer data points for 2019, as cohort constitution occurred across several regions of Switzerland in a step-wise fashion. For 2022, the analysis included only data collected until April 9, as the period of observation for this study was set to 3 years.

For each participant with at least two STI screenings, we calculated the time during which individuals were at

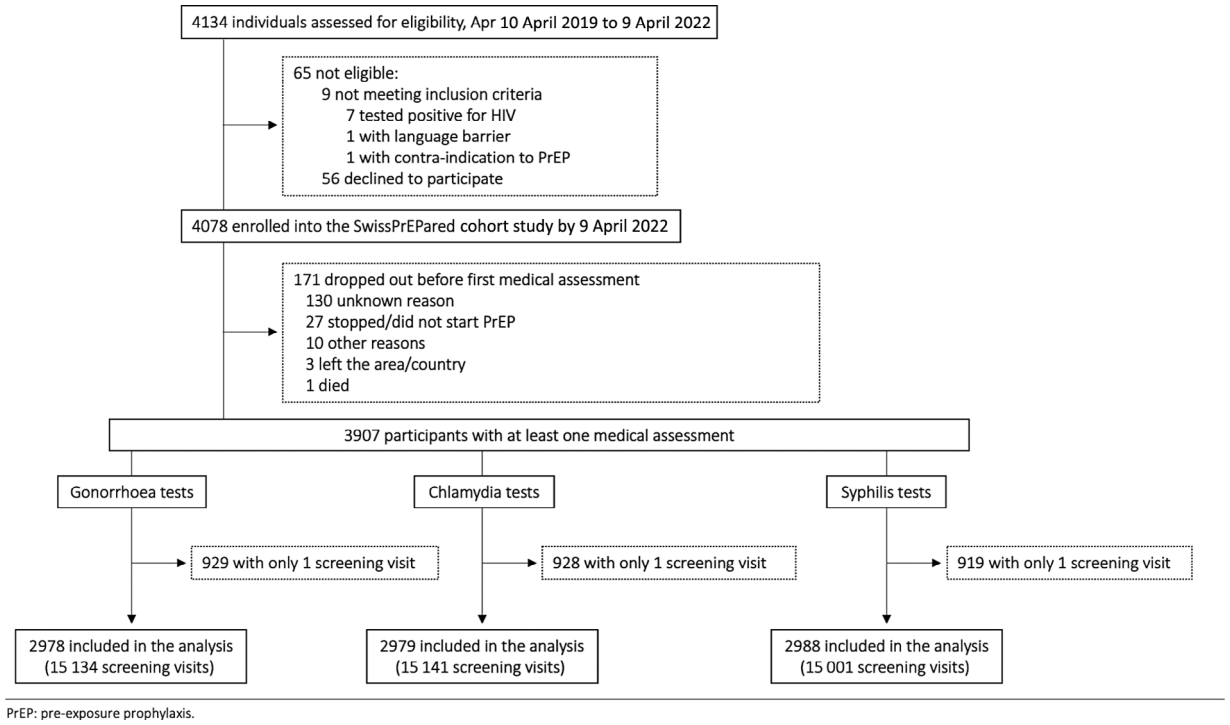

FIGURE 1 Study flow diagram. PrEP, pre-exposure prophylaxis.

risk of infection, which was defined as the time interval between study visits. In the case of a positive STI screening, we excluded 14 days after diagnosis from the time at risk, because we considered participants with a diagnosed and treated STI unlikely to be reinfected within 14 days. Incidence rates were calculated using the total number of infection diagnoses (events) in relation to the total number of person-years at risk. Estimates are expressed as events per 100 person-years with their corresponding 95% confidence intervals (CI).

To evaluate the association between STI diagnosis and behavioural factors, we used univariate and multivariable Cox proportional hazards models and calculated hazard ratios (HRs) with their corresponding 95% CI. To account for recurring infective events and time-varying covariates, we used the model proposed by Anderson and Gill [27, 28]. Right censoring occurred at last follow-up visit. The analysis exploring the association of condom use with casual partners and STI diagnosis was based on a subset of participants reporting sex with casual partners (in the previous 3 months). All multivariable models were adjusted for behavioural factors, the effect of time (i.e., calendar year as a categorical variable) and testing frequency, which was defined—for each participant—as the total number of tests divided by the individual's time at risk (as described elsewhere) [14]. Multivariable models included only visits with complete covariate data.

We also planned to explore the association of PrEP use and STI diagnosis. To that end, no Cox proportional hazards model was used, because the size of the control group (i.e., participants not taking PrEP due to refusal or lack of potential risk for HIV) was expected to be very small and prone to selection bias (given the nature of the cohort). Instead, we used univariable and multivariable logistic regressions with data from two different time points only, i.e., baseline and last follow-up visit. All multivariable logistic regressions were adjusted for behavioural factors, calendar year, and testing frequency.

Categorical variables were expressed as proportions, continuous variables as mean and standard deviation (SD) or median and interquartile range (IQR) (for non-normal distribution). Two-sided tests were performed, and a level of significance of 0.05 was used. All statistical analyses were conducted in R (version 4.1.3) [29].

RESULTS

Participants characteristics

Between 10 April 2019 and 9 April 2022, 4134 individuals were assessed for study eligibility (Figure 1). Of the 4078 participants enrolled into the SwissPrEPared cohort study, 171 withdrew before their first medical

TABLE 1 Participant characteristics at study start.

Characteristics	Overall ($n = 3907$)
Age, median [IQR]	39 [32–47]
Gender, *n* (%)	
Male	3801 (97.3)
Cis[a] male	3787 (99.6)
Trans[b] male	13 (0.3)
No answer	1 (0.1)
Female	57 (1.5)
Cis[a] female	15 (26.3)
Trans[b] female	39 (68.4)
Intersex-born female	3 (5.3)
Non-binary	41 (1.0)
Assigned male at birth	40 (97.6)
Assigned female at birth	1 (2.4)
None of the categories above	8 (0.2)
Sexual orientation, *n* (%)	
Homosexual	3399 (87.0)
Bisexual	334 (8.5)
Heterosexual	57 (1.5)
Not defined	117 (3.0)
Transmission group, n (%)	
MSM	3664 (93.8)
Cis[a] MSM	3652 (99.7)
Trans[b] MSM	12 (0.3)
Heterosexuals	56 (1.4)
Cis[a]	49 (87.5)
Trans[b]	7 (12.5)
Others	187 (4.8)
Highest education, *n* (%)	
University	1867 (47.8)
Higher education (not university)	797 (20.4)
High school/Baccalaureate	298 (7.6)
Apprenticeship	679 (17.4)
No or compulsory school only	134 (3.4)
Others	94 (2.4)
Missing data	38 (1.0)
Country of origin, *n* (%)	
Switzerland	2178 (55.7)
Germany	315 (8.1)
France	204 (5.2)
Brazil	132 (3.4)
Italy	102 (2.6)
Others (each <102 participants)	976 (25.0)
European countries	410 (42.0)
Non-European countries	566 (58.0)
Financial situation, *n* (%)	
Very comfortable	640 (16.4)
Comfortable	1891 (48.4)
Neither comfortable nor difficult	948 (24.3)
Difficult	286 (7.3)
Very difficult	141 (3.6)
Missing data	1 (0.0)
Number of sexual partners (since last visit), n (%)	
0 to 2	1542 (39.5)
3 to 10	1778 (45.5)
More than 10	586 (15.0)
Sex with casual partners, *n* (%)	3227 (82.6)
Condom use with casual partners, *n* (%)	*n = 3227*
Never	668 (20.7%)
Sometimes	997 (30.9%)
Mostly	819 (25.4%)
Always	743 (23.0%)
Current smoker, *n* (%)	1164 (29.8)
Chemsex substances use, *n* (%)	414 (10.6)
Already taking PrEP at study start, *n* (%)	1742 (44.6)
Ever took PrEP, *n* (%)	1763 (45.1)
Ever took HIV post-exposure prophylaxis, *n* (%)	998 (25.5)
Previous lifetime STI diagnosis, self-reported, *n* (%)	2554 (65.4)
Gonorrhoea[c]	1690 (35.0)
Chlamydia[c]	1500 (31.1)
Syphilis[c]	928 (19.2)
Others[c]	706 (14.6)

Note: Recall period for behavioural variables was 3 months, unless otherwise specified.

Abbreviations: IQR, interquartile range; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection.

[a]Cis refers to individuals for whom sex assigned at birth matches gender identity.

[b]Trans refers to a discrepancy between sex assigned at birth and the reported gender identity.

[c]Numbers do not add since participants may report several previous STIs.

assessment. Of the remaining 3907 participants, 2978 had at least two screening visits for gonorrhoea, 2979 had visits for chlamydia, and 2988 had visits for

TABLE 2 Prevalence and incidence of sexually transmitted infections in the SwissPrEPared cohort.

Prevalence at study start	Number of infections	Number of participants	Prevalence (95% CI)
Gonorrhoea	256	3907 participants	6.6 (5.8–7.4)
Chlamydia	256	3907 participants	6.6 (5.8–7.4)
Syphilis (active/latent cases)	78	3841 participants	2.0 (1.6–2.5)
Incidence rate	**Number of infections**	**Total follow-up time (in person-years)**	**Incidence per 100 person-years (95% CI)**
Gonorrhoea	**867**	**3815.7**	**22.8 (21.3–24.4)**
2019	19	52.6	36.1 (21.8–56.4)
2020	221	932.3	23.7 (20.7–27.0)
2021	480	2146.6	22.4 (20.4–24.5)
2022	147	675.0	21.8 (18.4–25.6)
Chlamydia	**1001**	**3802.5**	**26.3 (24.7–28.0)**
2019	21	52.7	39.9 (24.7–61.0)
2020	260	933.0	27.9 (24.6–31.5)
2021	553	2143.6	25.8 (23.7–28.0)
2022	167	673.3	24.8 (21.2–28.9)
Syphilis (active/latent cases)	**170**	**3858.6**	**4.4 (3.8–5.1)**
2019	3	52.4	5.7 (1.2–16.7)
2020	41	949.0	4.3 (3.1–5.9)
2021	95	2163.8	4.4 (3.6–5.4)
2022	31	693.5	4.5 (3.0–6.4)
Any of the STIs outlined above	**2038**	**3858.6**[a]	**52.8 (50.6–55.2)**
2019	43	52.7	81.6 (59.1–109.9)
2020	522	949.0	55.0 (50.4–59.9)
2021	1128	2163.8	52.1 (49.1–55.3)
2022	345	693.5	49.8 (44.6–55.3)

Abbreviations: CI, confidence interval; STI, sexually transmitted infection.
[a]The longest available period of time was used to calculate the incidence of all STIs.

syphilis. The final analysis included 15 134 screening visits for gonorrhoea, 15 141 for chlamydia, and 15 001 for syphilis.

At study start, included participants were aged 18 to 78 years (median 39, IQR 32–47), and most identified as MSM ($n = 3664$ [93.8%]) (Table 1). The majority were born in Switzerland ($n = 2178$ [55.7%]), had completed a university degree ($n = 1867$ [47.8%]), and reported having a comfortable financial situation ($n = 1891$ [48.4%]). At study start, 44.6% ($n = 1742$) reported current PrEP use. Most participants reported 3 to 10 partners ($n = 1778$ [45.5%]) since their last visit. Sex with casual partners was observed in 3227 participants (82.6%), during which 668 (20.7%) never used condoms. Chemsex substance use was found in 414 participants (10.6%).

Primary outcome

The prevalence of STIs at study start was 6.6% for gonorrhoea, 6.6% for chlamydia, and 2.0% for syphilis (Table 2). Total follow-up time was 3815.7 person-years for gonorrhoea, 3802.5 person-years for chlamydia, and 3858.6 person-years for syphilis. The median time between testing visits was 91 days (IQR 37–113) for gonorrhoea, 90 days (IQR 38–112) for chlamydia, and 91 days (IQR 41–116) for syphilis. The incidence of STI is outlined in Table 2 (22.8 per 100 person-years for gonorrhoea, 26.3 for chlamydia, and 4.4 for syphilis). The overall STI incidence was 52.8 per 100 person-years. Yearly incidence rates for gonorrhoea, chlamydia, and syphilis decreased over time.

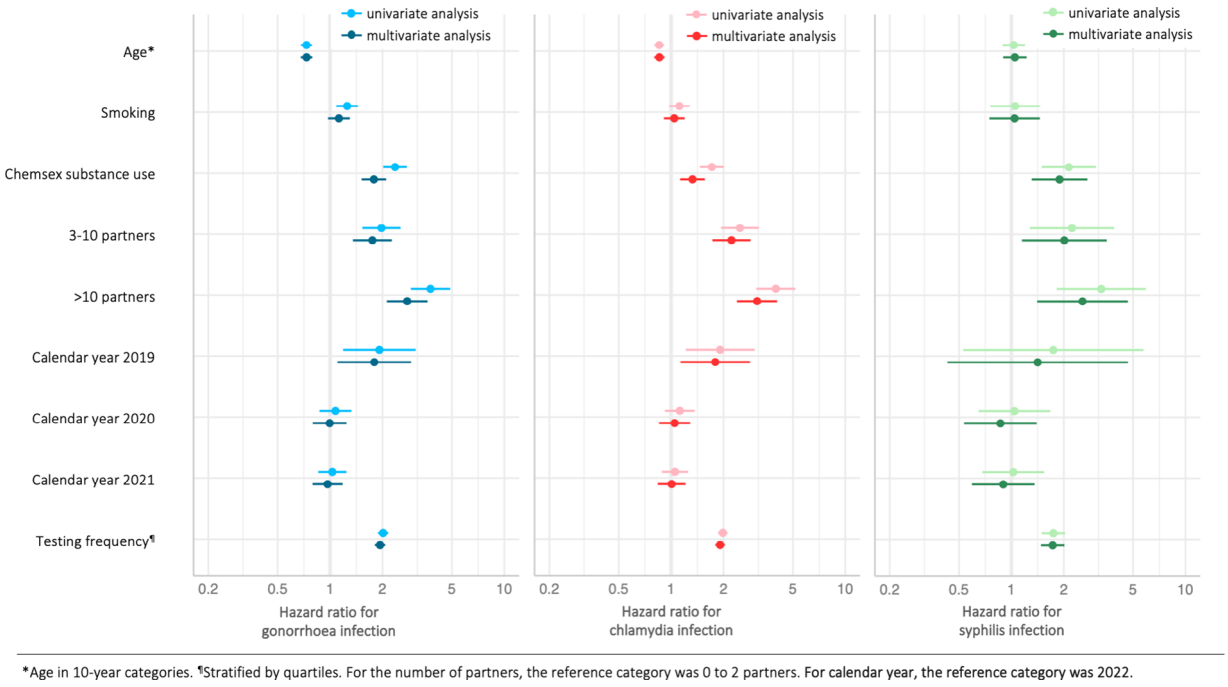

FIGURE 2 Unadjusted versus adjusted hazard ratios for the association of sexually transmitted infections with behavioural factors.

TABLE 3 Unadjusted versus adjusted hazard ratios for the association of sexually transmitted infections with behavioural factors and other covariates.

	Gonorrhoea				Chlamydia				Syphilis (active + latent)			
	Univariate analysis		Multivariable analysis		Univariate analysis		Multivariable analysis		Univariate analysis		Multivariable analysis	
Factor	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Age[a]	0.73	0.68–0.79	0.73	0.68–0.79	0.85	0.79–0.92	0.86	0.80–0.92	1.03	0.89–1.20	1.05	0.90–1.22
Smoking	1.25	1.07–1.47	1.12	0.97–1.30	1.11	0.96–1.30	1.04	0.90–1.21	1.05	0.75–1.47	1.04	0.76–1.44
Chemsex substance use	2.36	2.00–2.79	1.78	1.52–2.10	1.71	1.44–2.04	1.33	1.11–1.58	2.14	1.49–3.07	1.89	1.31–2.72
Partner number 3 to 10	1.97	1.54–2.52	1.75	1.37–2.24	2.48	1.92–3.21	2.22	1.71–2.88	2.23	1.28–3.89	2.01	1.15–3.52
Partner number >10	3.77	2.91–4.88	2.77	2.13–3.60	3.98	3.03–5.23	3.11	2.36–4.09	3.28	1.82–5.93	2.56	1.40–4.69
Calendar year 2019	1.92	1.15–3.19	1.79	1.12–2.88	1.91	1.17–3.13	1.79	1.09–2.96	1.74	0.39–7.86	1.42	0.31–6.57
Calendar year 2020	1.07	0.87–1.33	0.99	0.79–1.25	1.12	0.92–1.37	1.05	0.85–1.29	1.04	0.65–1.67	0.86	0.53–1.41
Calendar year 2021	1.03	0.86–1.24	0.97	0.80–1.17	1.05	0.88–1.25	1.01	0.84–1.21	1.03	0.68–1.54	0.90	0.59–1.36
Testing frequency[b]	2.02	1.88–2.16	1.94	1.80–2.08	1.98	1.86–2.12	1.91	1.79–2.04	1.74	1.49–2.04	1.73	1.47–2.02

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]In 10-year categories.

[b]Stratified by quartiles. For partner number, the reference category was 0 to 2 partners. For calendar year, the reference category was 2022.

Additional analyses

In the analysis evaluating the association of STI diagnosis with behavioural factors, participants with complete covariate data contributed to 11 913 screening visits for gonorrhoea (845 infections), 11 916 for chlamydia (978 infections), and 11 776 for syphilis (169 infections). In the univariate analysis of gonorrhoea and chlamydia, all covariates were independently associated with STI diagnosis, except for calendar years 2020 and 2021 and for smoking (for chlamydia) (Figure 2; Table 3). For syphilis, there was a significant association for chemsex substance use and the number of partners. In the multivariable analysis, factors that were associated with a higher risk of gonorrhoea and chlamydia diagnosis were calendar

year 2019, chemsex substance use, and the number of partners. For the latter, there was an incremental increase in risk according to the category of interest. The HRs decreased with age. A large drop between 2019 and 2020, followed by a smaller decrease over time, was observed with calendar year. For syphilis, significant associations were found with chemsex substance use and the number of partners.

In the analysis exploring the association of STIs with condom use for casual sex, participants with complete covariate data contributed to 10 530 screening visits for gonorrhoea (794 infections), 10 533 visits for chlamydia (925 infections), and 10 290 visits for syphilis (161 infections). In the multivariable analysis, all effect estimates were >1.0, indicating a higher risk of STI diagnosis when condoms were not systematically used (Table S1). However, significant associations were found only for the last two frequency categories (i.e., "sometimes" and "never") in the gonorrhoea and chlamydia analyses. Additionally, there was no incremental risk increase across condom use categories (i.e., HR "mostly" < HR "sometimes" < HR "never"). To further explore this, each model was stratified by the number of partners categories. However, these analyses yielded inconsistent results, since sample sizes within strata were small and/or the event rate was particularly low (Table S2). Finally, we investigated the association of PrEP use with STI diagnosis at two different time points. In the adjusted model for baseline, participants taking PrEP were more likely to be diagnosed with gonorrhoea or chlamydia but not syphilis (Table S3). At last visit, participants not taking PrEP contributed to a very small number of visits; there was no association of PrEP use with STI diagnosis, except for chlamydia.

DISCUSSION

In this longitudinal analysis including data from nearly 3000 participants, the incidence rate for gonorrhoea, chlamydia, or syphilis was 52.8 per 100 person-years. There was a trend towards lower incidences of STIs over time, which was confirmed in a time-to-event analysis adjusting for multiple risk factors. Among participants reporting chemsex substances use and multiple sexual partners, the risk of being diagnosed with gonorrhoea, chlamydia, or syphilis was markedly increased. Similar findings were observed in younger participants, who were at higher risk of gonorrhoea or chlamydia. In contrast, the association of condom use frequencies with STI diagnosis was inconsistent.

The STI incidence rates found in this study were lower than in other PrEP cohorts [15, 24, 30–33] but exceeded those observed previously among MSM between 2016 and 2017 in Switzerland [34]. A first reason for the lower incidence could be less frequent STI testing. However, in our study, screening was performed on average every 3 months, and this time interval was comparable to that in other PrEP cohorts exhibiting higher STI incidence rates [30, 33]. It is therefore unlikely that the lower rates observed in our study would be related to less frequent testing—our results rather suggest that a systematic "test and treat" strategy may lead, in the long term, to a decline in STI incidences. Another explanation could be that our study participants had a lower baseline risk for STIs. A recent analysis of the Australian PrEPX study reported a decline in STI incidences, possibly related to a progressive decrease in STI baseline risk among PrEP adopters [33]. The main assumptions behind this phenomenon were changes in the size and constituents of sexual networks as PrEP roll-out progressed, which may have impacted STI transmission [15, 33]. In our study, nearly 45% of study participants were taking PrEP at baseline, which was markedly less than that in a previous analysis of the SwissPrEPared cohort performed 10 months after study inception (75.5%) [5]. A comparable downward trend was observed for chemsex substance use, number of partners, and STI prevalence (Table S4). Thus, similar to the phenomenon observed in Australia, changes occurring in local sexual networks as PrEP uptake in Switzerland progressed may have affected the underlying baseline risk for STIs and hence the profile of participants entering our study. This may explain the overall lower incidence rates observed in our cohort compared with studies reporting rates captured at an earlier stage of PrEP implementation. A figure outlining the baseline STI risk in our cohort participants is provided in Figure S1, as this may be of interest for future research on sexual networks in the context of PrEP.

In this longitudinal analysis of the SwissPrEPared cohort, we captured behavioural data retrieved from approximately 15 000 PrEP visits, which yielded more than 3800 person-years of follow-up. Using a statistical approach that accounted for time-varying covariates, we showed that the use of methamphetamine, mephedrone, or GHB/GBL in a sexual context was strongly associated with STI diagnosis, and this effect was robust to adjustment for other behavioural factors, testing frequency, and time trends. Other risk factors included younger age and multiple sexual partners. Consistent with a previous study conducted in MSM with primary HIV infection [35], these results suggest that our cohort included individuals with a particular risk profile experiencing high rates of STIs. These findings have direct implications in daily PrEP care, as they may help identify vulnerable populations and shape tailored prevention measures within

prevention programmes. On this basis, the SwissPrEPared programme is currently implementing free STI screening for subgroups deemed at higher STI risk in some centres. Other measures could include tailored services for sex workers, transgender people, or migrants.

In this study, although less frequent condom use was significantly associated with STI diagnosis, the strength of the association was not consistent across frequency categories: instead of an incremental risk increase with lessening frequency, never-users had a lower risk of STI than those reporting more frequent use (i.e., "sometimes" or "mostly"). Several reasons may explain the lack of incremental effect observed in our study. First, with the development of effective HIV treatment, the proven efficacy of "U = U", and the wider availability of PrEP, systematic condom use has been substantially declining over the past two decades [16]. Other behavioural trends, such as changes in serosorting, in sexual practices (e.g. condomless oral sex, rimming), or in the way sexual partners are met (e.g. dating applications), may have gained further relevance in the context of STI acquisition [15, 16]. Our analysis seems thus to suggest that condom use—in the form of four frequency categories—may not be appropriate to capture the underlying behavioural pattern leading to an increased STI risk. Another reason for the lack of incremental risk increase could be related to PrEP access: because PrEP prescription was—at least at study inception—based on risk stratification, response/social desirability bias may have occurred to some extent, since reporting no condom use would increase participants' chances to qualify for PrEP prescription. However, with time less stringent prescription criteria are being applied, and the effect of this potential source of bias should lessen as the study progresses. Finally, from a probabilistic perspective, the likelihood to never use condoms would be larger in participants with a lower number of partners (assuming the lower number of partners would reflect a lower number of sexual acts). As suggested by a previous study conducted among multi-partner MSM in Switzerland [34], the number of partners seems to have a much larger effect on STI acquisition than condom use.

Nevertheless, this study has some limitations. First, in the models assessing the association of behavioural factors with the risk of syphilis, the large CIs must be interpreted in the light of low event rates. Further assessments of the SwissPrEPared cohort will confirm or refute the lack of significant effect observed here for some behavioural factors. Second, the time trend towards fewer infections must be interpreted with caution, since our analysis included visits performed during the SARS-CoV-2/COVID-19 pandemic: in a previous analysis of the SwissPrEPared cohort, we found that sexual behaviour and access to PrEP care might have been affected during the different phases of the pandemic [36]. However, our findings seem robust to the possible confounding effect of the pandemic, since our approach accounted for time-varying confounders and all models were adjusted for several potential confounders relevant to the pandemic. Third, the analysis exploring the association between PrEP use and STI diagnosis was hampered by the lack of a proper control group (due to the decline of PrEP non-users over time). Further in-depth analysis revealed that participants who never took PrEP over the entire study time were less likely to be screened for STIs and had longer time intervals between study visits (Table S5). Thus, future studies addressing the association between PrEP use and STI diagnosis should take these two limiting factors into account. Fourth, although many centres offer extended opening hours for PrEP counselling and STI testing, we cannot exclude that some participants may have accessed STI testing, diagnosis, and treatment outside the SwissPrEPared study. It can thus be that some incident infections were not captured by our analysis. However, as the number of participating centres is growing (i.e., 32 as of May 2022), fewer events are expected to be missed over time. Finally, our analysis did not consider participants with only one screening visit, which led to the exclusion of nearly 1000 participants. However, in a previous analysis of the SwissPrEPared cohort [5], we found that participants who withdrew after baseline assessment had a different risk profile, i.e. they had fewer sexual partners, were more likely to always use condoms with casual partners, were less likely to report previous lifetime STIs or substance use in a sexual context, and had a lower prevalence of STIs at baseline. Overall, these findings tend to indicate that, had participants with only one screening visit been included in the analysis, this would have led to an underestimation of the true STI risk, since the excluded participants seem to be generally at lower risk of STIs.

In this longitudinal analysis including data from more than 15 000 screening visits, we found a downward trend in STI incidences over time. The risk of STI diagnosis was markedly increased among younger participants and those reporting multiple sexual partners and the use of chemsex substances. Overall, the findings presented in this work may help clinicians involved in PrEP care shape prevention measures tailored to vulnerable populations at higher risk of STI.

AUTHOR CONTRIBUTIONS

Frédérique Hovaguimian, Roger D. Kouyos, Jan S. Fehr, and Benjamin Hampel participated in study conception and design, data acquisition and interpretation, and critical revision of the manuscript. Frédérique Hovaguimian drafted the first manuscript. Frédérique Hovaguimian, Roger D. Kouyos, and Katharina Kusejko performed the statistical analyses. Axel J. Schmidt, Enos Bernasconi,

Dominique L. Braun, Alexandra Calmy, Julia Notter, Marcel Stoeckle, Bernard Surial, Vanessa Christinet, Katharine E.A. Darling, Carsten Depmeier, Severin Läuchli, Emmanuelle Boffi El Amari, and Manuela Rasi participated in data acquisition and critical revision of the manuscript. Axel J. Schmidt, Matthias Reinacher, Dunja Nicca, Philip Bruggmann, David Haerry, Raphaël Bize, Nicola Low, Florian Vock, Jürg Böni, Philip E. Tarr, and Philipp P. Bosshard participated in study conception and design and critical revision of the manuscript. All authors have read the manuscript, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission.

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CONFLICTS OF INTEREST

BH has received payments for advisory boards, lectures and travel grants from Gilead Sciences and ViiV Healthcare. The institution of RDK received a research grant from Gilead Sciences. The institution of JSF has received research and programme grants from Gilead Sciences, Merck, and ViiV Healthcare. DLB has received, outside of the submitted work, honoraria and/or financial support for advisory boards, lectures, and travel grants from Gilead, Merck, ViiV, AbbVie, Pfizer, and Astra Zeneca. KEAD's institution has received research support from Gilead Sciences and MSD, both unrelated to this publication. PET's institution has received research and educational grants from Gilead Sciences, Merck, and ViiV Healthcare. EB's institution has received research grants from Merck and payments for EB's participation in advisory boards, as well as travel grants, from Gilead Sciences, Merck, ViiV Healthcare, Pfizer, Astra Zeneca, and AbbVie. PBr's institution has received project, research, and travel grants from Gilead and AbbVie. BS reports support to his institution for advisory boards and travel grants from Gilead Sciences and ViiV, outside of the present work. DH's institution received unconditional grants from AbbVie, Gilead Sciences, MSD, and ViiV Healthcare. DH has received payments for advisory boards from Gilead Sciences and ViiV Healthcare. The institution of FV received programme grants and sponsoring from Gilead Science and ViiV Healthcare and payments for FV's participation in advisory boards and conferences from Gilead Science, ViiV Healthcare, and Teva Pharma. The institution of FV received programme grants and sponsoring from Gilead Science and ViiV Healthcare and payments for FV's participation in advisory boards and conferences from Gilead Science, ViiV Healthcare, and Teva Pharma. The other authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

Datasets analyzed during the current study and used to generate tables, figures, and the supplementary material are not publicly available due to the sensitive nature of the data yielded by this highly representative, individual-level dataset. Source data are thus not provided with this paper. Investigators with a request for selected data should send a proposal to the SwissPrEPared e-mail address (info@swissprepared.ch). The provision of data will be considered by the Scientific Board of the SwissPrEPared cohort study and the relevant study team. Data provision is subject to Swiss legal and ethical regulations and will be detailed in a material and data transfer agreement.

ETHICS APPROVAL AND PATIENT CONSENT STATEMENT

The SwissPrEPared study was approved by all local ethical committees (lead committee: Zurich, Switzerland—registration number 2018–02015). Written informed consent was obtained from all participants.

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REFERENCES

1. 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(27):2587-2599.
2. 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(10013):53-60.
3. Molina JM, Capitant C, Spire B, et al. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. *N Engl J Med*. 2015;373(23):2237-2246.
4. Schaefer R, Schmidt HA, Ravasi G, et al. Adoption of guidelines on and use of oral pre-exposure prophylaxis: a global summary and forecasting study. *Lancet HIV*. 2021;8(8):e502-e510.
5. Hovaguimian F, Martin E, Reinacher M, et al. Participation, retention and uptake in a multicentre pre-exposure prophylaxis cohort using online, smartphone-compatible data collection. *HIV Med*. 2022;23(2):146-158.
6. Brown AE, Mohammed H, Ogaz D, et al. Fall in new HIV diagnoses among men who have sex with men (MSM) at selected London sexual health clinics since early 2015: testing or treatment or pre-exposure prophylaxis (PrEP)? *Euro Surveill*. 2017;22(25):30553.
7. Buchbinder SP, Havlir DV. Getting to zero San Francisco: a collective impact approach. *J Acquir Immune Defic Syndr*. 2019;82(suppl 3):S176-S182.
8. Nwokolo N, Hill A, McOwan A, Pozniak A. Rapidly declining HIV infection in MSM in Central London. *Lancet HIV*. 2017;4(11):e482-e483.
9. Whitlock G, Scarfield P, Dean Street Collaborative Group. HIV diagnoses continue to fall at 56 dean street. *EClinicalMedicine*. 2020;19:100263.
10. Estcourt C, Yeung A, Nandwani R, et al. Population-level effectiveness of a national HIV preexposure prophylaxis programme in MSM. *Aids*. 2021;35(4):665-673.
11. Grulich AE, Guy R, Amin J, et al. Population-level effectiveness of rapid, targeted, high-coverage roll-out of HIV pre-exposure prophylaxis in men who have sex with men: the EPIC-NSW prospective cohort study. *Lancet HIV*. 2018;5(11):e629-e637.
12. Sullivan PS, Phaswana-Mafuya N, Baral SD, et al. HIV prevalence and incidence in a cohort of south African men and transgender women who have sex with men: the Sibanye methods for prevention packages Programme (MP3) project. *J Int AIDS Soc*. 2020;23(Suppl 6):e25591.
13. Kojima N, Davey DJ, Klausner JD. Pre-exposure prophylaxis for HIV infection and new sexually transmitted infections among men who have sex with men. *Aids*. 2016;30(14):2251-2252.
14. 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(14):1380-1390.
15. Nguyen VK, Greenwald ZR, Trottier H, et al. Incidence of sexually transmitted infections before and after preexposure prophylaxis for HIV. *Aids*. 2018;32(4):523-530.
16. Chow EPF, Grulich AE, Fairley CK. Epidemiology and prevention of sexually transmitted infections in men who have sex with men at risk of HIV. *Lancet HIV*. 2019;6(6):e396-e405.
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(4):358-364.
18. 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(5):676-686.
19. MacGregor L, Speare N, Nicholls J, et al. Evidence of changing sexual behaviours and clinical attendance patterns, alongside increasing diagnoses of STIs in MSM and TPSM. *Sex Transm Infect*. 2021;97(7):507-513.
20. Jain JP, Gyamerah AO, Baguso GN, Dawson-Rose C, Ikeda J, Santos GM. Social and behavioral correlates of sexually transmitted infections among men who have sex with men who use alcohol in the San Francisco Bay Area. *Am J Mens Health*. 2021;15(3):15579883211026830.
21. Carlo Hojilla J, Koester KA, Cohen SE, et al. Sexual behavior, risk compensation, and HIV prevention strategies among participants in the San Francisco PrEP demonstration project: a qualitative analysis of counseling notes. *AIDS Behav*. 2016;20(7):1461-1469.
22. Marcus JL, Glidden DV, Mayer KH, et al. No evidence of sexual risk compensation in the iPrEx trial of daily oral HIV preexposure prophylaxis. *PloS One*. 2013;8(12):e81997.
23. 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(5):712-718.
24. Werner RN, Gaskins M, Nast A, Dressler C. Incidence of sexually transmitted infections in men who have sex with men and who are at substantial risk of HIV infection—a meta-analysis of data from trials and observational studies of HIV pre-exposure prophylaxis. *PloS One*. 2018;13(12):e0208107.
25. World Health Organization. *Prevention and Control of Sexually Transmitted Infections (STIs) in the Era of Oral Pre-Exposure Prophylaxis (PrEP) for HIV*. WHO; 2019.
26. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. *Epidemiology*. 2007;18(6):805-835.
27. Amorim LD, Cai J. Modelling recurrent events: a tutorial for analysis in epidemiology. *Int J Epidemiol*. 2015;44(1):324-333.
28. Andersen PK, Gill RD. Cox's regression model for counting processes: a large sample study. *Annals Stat*. 1982;10(4):1100-1120.
29. R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing; 2021.
30. Hoornenborg E, Coyer L, Achterbergh RCA, et al. Sexual behaviour and incidence of HIV and sexually transmitted infections among men who have sex with men using daily and event-driven pre-exposure prophylaxis in AMPrEP: 2 year results from a demonstration study. *Lancet HIV*. 2019;6(7):e447-e455.
31. 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(1):75-84.

32. Zeggagh J, Bauer R, Delaugerre C, et al. Incidence and risk factors for recurrent sexually transmitted infections among MSM on HIV pre-exposure prophylaxis. *Aids*. 2022;36(8):1129-1134.
33. Traeger MW, Guy R, Asselin J, et al. Real-world trends in incidence of bacterial sexually transmissible infections among gay and bisexual men using HIV pre-exposure prophylaxis (PrEP) in Australia following nationwide PrEP implementation: an analysis of sentinel surveillance data. *Lancet Infect Dis*. 2022; 22(8):1231-1241.
34. Schmidt AJ, Rasi M, Esson C, et al. The swiss STAR trial—an evaluation of target groups for sexually transmitted infection screening in the sub-sample of men. *Swiss Med Wkly*. 2020;150: w20392.
35. Braun DL, Marzel A, Steffens D, et al. High rates of subsequent asymptomatic sexually transmitted infections and risky sexual behavior in patients initially presenting with primary human immunodeficiency Virus-1 infection. *Clin Infect Dis*. 2018;66(5): 735-742.
36. Winter BL, Hovaguimian F, Kouyos RD, et al. Changes in mental and sexual health among MSM using HIV pre-exposure prophylaxis during the SARS-CoV-2 pandemic: longitudinal analysis of the SwissPrEPared cohort study. *Swiss Med Wkly*. 2022;152:w30192.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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