

Very Low Incidence of HIV-infection and Decreasing Incidence of STI Among PrEP Users in 2020 After Introduction of Health Insurance Coverage in Germany

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Research Article

Keywords: HIV-infection, PrEP users, health insurance coverage, STI, Germany, low incidence

Posted Date: January 13th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1201597/v1>

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Abstract

Introduction

Objectives of this study, as part of a nation-wide HIV pre-exposure prophylaxis (PrEP) evaluation project, were to determine the incidence and prevalence of infections with HIV, Chlamydia, Gonorrhea, Syphilis, Hepatitis A/B/C in persons using PrEP, and to describe the health care funded PrEP use in Germany. Additionally, factors associated with Chlamydia/Gonorrhea and Syphilis infections were assessed.

Methods

Anonymous data of PrEP users were collected at HIV-specialty centers from 09/2019-12/2020. Incidence rates were calculated per 100 person years (py). Logistic regression was used to analyze risk factors associated with sexually transmitted infections (STIs).

Results

4620 PrEP users were included: 99.2% male, median age 38 years (IQR 32-45), PrEP indication 98.6% men who have sex with men (MSM). Duration of PrEP use were 5132 py; median duration 451 days (IQR 357-488).

Four HIV infections were diagnosed, incidence rate 0,078/100py (95% CI 0.029-0.208). For two suboptimal adherence was reported and in the third case suboptimal adherence and resistance to emtricitabine was observed. One infection was likely acquired before PrEP start.

Incidence rates were 21.6/100py for Chlamydia, 23.7/100py for Gonorrhea, 10.1/100py for Syphilis and 55.4/100py for any STI and decreased significantly.

65.5% of Syphilis, 55.6% of Chlamydia and 50.1% of Gonorrhea cases were detected by screening of asymptomatic individuals.

In a multivariable analysis among MSM younger age, PrEP start before health insurance coverage and daily PrEP were associated with greater risk for Chlamydia/Gonorrhea. Symptom triggered testing and a history of STI were associated with a higher risk for Chlamydia/Gonorrhea and Syphilis.

Conclusions

We found that HIV-PrEP is almost exclusively used by MSM in Germany. A very low incidence of HIV-infection and decreasing incidence rates of STIs were found in this cohort of PrEP users. The results were likely influenced by the SARS-CoV-2 pandemic. Rollout of PrEP covered by health insurance should be continued to prevent HIV infections. Increased PrEP availability to people at risk of HIV infection through the elimination of barriers requires further attention. Investigation and monitoring with a longer follow-up would be of value.

Introduction

Infection with the human immunodeficiency virus (HIV) remains globally endemic with 1,5 million new infections annually despite continued advancements in its management, treatment, and prophylaxis (1). In Germany, HIV transmission remains an issue despite prophylactic measures, and a knowledgeable men who have sex with men (MSM) population which is the largest affected group (2). Whereas prevention historically focused on condom use and safe injection practices, the approval of the antiviral agents tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) for HIV pre-exposure prophylaxis (PrEP) has added a valuable tool for prevention in certain populations. Efficacy has been reported as high as 95 percent in MSM (3). Unfortunately, similar results were not observed in women (4). Since the efficacy of PrEP is highly correlated with adherence, an evaluation in the routine clinical care setting would provide further information on PrEP use and outcomes (5).

Although the use of PrEP significantly reduces the risk of HIV transmission, it may change sexual behavior entailing an elevated risk for the transmission of other sexually transmitted infections (STIs) and even HIV (6–8). On the other hand, PrEP access under medical supervision offers an opportunity for counselling, regular STI screening and appropriate treatment (6). Earlier diagnosis of HIV infection and STIs and prompt treatment in turn may limit onward transmission.

PrEP was approved in Germany in 2016 and available initially on a self-paying basis (9). As a result, it was frequently obtained from informal sources outside of the health care system and hence without adequate testing for HIV and other STIs, counselling and monitoring of side effects. Since September 2019, PrEP and its care through a certified and (HIV-) specialized physician is covered by the statutory health care system in Germany (10).

The uptake and outcome of PrEP coverage by statutory health care as well as effects on STIs have been evaluated through a nation-wide study in Germany ("EvE-PrEP" project). The evaluation consisted of several independent studies. Objectives of the NEPOS (National Evaluation of PrEP Outcomes and STIs) study, as part of the EvE-PrEP project, was to determine the incidence and prevalence of infections with HIV, Chlamydia, Gonorrhea, Syphilis, Hepatitis A/B/C in persons using PrEP, and to describe the health care funded PrEP use in Germany. Additionally, factors associated with infections with Chlamydia/Gonorrhea and Syphilis were assessed.

Methods

The NEPOS study was conducted by the Robert Koch Institute (RKI) in collaboration with the German association of physicians in HIV-care (dagnä e.V.). All HIV-specialty practices and ambulatory care centers were invited to participate. The maximal number of PrEP users that could be documented in the study was set at 5000. To ensure that the study population represents the PrEP using population as a whole, the centers were allotted a defined quota on the basis

of their PrEP using population in reference to that of all participating centers. Only persons with PrEP start prior to April 1st, 2020, could be recruited into the study.

Data were collected anonymously using an electronic reporting form in the first quarter of 2021 retrospectively for the time-period of September 2019 through December 2020. PrEP start prior to September 2019 was also documented. Data included patient characteristics (age, gender), PrEP use (indication, starting date, duration, continuous vs. on-demand use as well as any interruptions or discontinuations and reasons), testing for and potential diagnosis of HIV, hepatitis and STI, as well as hepatitis antibody status. Aside from HIV-infection, STI included Chlamydia, Gonorrhea and Syphilis. Viral Hepatitis included A, B and C. The study duration was divided into five time intervals: one September through December 2019, then four quarters in 2020. STI were documented for each time interval, HIV and hepatitis with a date of diagnosis.

In addition to recording PrEP use at the individual level, a separate study center survey provided information on PrEP use and delivery, including the total number of PrEP users and HIV-positive patients in care.

In accordance with other studies STI diagnosis within 90 days of PrEP initiation was defined as baseline prevalence (11). Incidence rates were determined for STIs occurring while on PrEP and calculated by dividing the number of STI cases by the duration of PrEP exposure per time interval per 100 person years (py). For incidence rates of infections with hepatitis and HIV, the duration of PrEP exposure in the observation period to the date of diagnosis was calculated as person-time. More than one positive test for a certain STI within one time interval was counted as one result. It was predefined that PrEP was only considered interrupted or discontinued if stopped for longer than four weeks. PrEP pill coverage was calculated using the number of days prescribed divided by the number of days on PrEP.

Univariable and multivariable mixed effects logistic regression was used to analyze risk factors associated with infections with Chlamydia/Gonorrhea and Syphilis. The analysis was performed among all MSM with/without other risk factors being tested in the respective time interval adjusted for age, PrEP use (on-demand/daily), PrEP interruptions, PrEP discontinuations, PrEP duration, number of PrEP intervals under observation, PrEP start before statutory health insurance coverage, infections with Hepatitis or HIV, other STI than the one analyzed, STI history in the past six months before PrEP start, the number of STI tests, observation within or before the covid-19 pandemic period.

Data were collected and prepared using a MS-SQL server. Statistical analysis was performed using STATA Version 17. Figures were produced using GfK RegioGraph and Microsoft Excel (Office 2019).

Results

Forty-seven German HIV-specialty practices and ambulatory care centers participated in the study and provided representation of PrEP use as a whole from both a geographical and a diversity perspective (figure 1).

4620 PrEP users were recruited into this study. Nearly all (99.2%) were male, median age was 38 years (IQR 32-45), PrEP indication was MSM for 98.6% of whom 10.6% had additional risk factors. Of the 39 PrEP users who were not male, 17 were female, 16 transgender and four non-binary gender. Characteristics are shown in Table 1. The majority of cases (n=1638, 35.5%) were documented in Berlin, which also reflects the pre-dominant location of current PrEP use (4775 PrEP users of the 22 366 cared for in all study centers).

Table 1
Characteristics of the study population

Total study population 4620		N	(%)
Age (years)	16-19	3	(0.1%)
	20-29	715	(15.5%)
	30-39	1864	(40.3%)
	40-49	1233	(26.7%)
	50-59	669	(14.5%)
	≥60	136	(2.9%)
Gender	Male	4581	(99.2%)
	Female	17	(0.4%)
	Diverse	4	(0.1%)
	Trans (m->f)	12	(0.3%)
	Trans (f->m)	6	(0.1%)
PrEP indication	MSM	4065	(88.0%)
	MSM & other high risk contacts	294	(6.4%)
	MSM & HIV-discordant couple	142	(3.1%)
	Other high risk contacts	33	(0.7%)
	MSM & IDU	25	(0.5%)
	HIV-discordant couple	23	(0.5%)
	IDU	1	(0.0%)
	Other combinations	33	(0.7%)
	Missing	4	(0.1%)
PrEP type of administration	Continuous	3737	(80.9%)
	On Demand	874	(18.9%)
	Missing	9	(0.2%)
PrEP start prior to 01/09/2019	Yes	2466	(53.4%)
	No	2106	(45.6%)
	Unknown / missing	48	(1.0%)
PrEP interruption	No	4159	(90.0%)
	Yes	461	(10.0%)
PrEP discontinuation	No	4012	(86.8%)
	Yes	608	(13.2%)
Calculated PrEP pill coverage – PrEP prescriptions/time	<0.75	1069	(23.1%)
	0.75 – 1.24	3184	(68.9%)
	≥1.25	367	(7.9%)
	Missing	26	(0.6%)
Hepatitis A immunity	Yes	3358	(72.7%)
	Incomplete	201	(4.4%)
	No	299	(6.5%)
	Not determined / missing	762	(16.5%)

Total study population 4620		N	(%)
Hepatitis B immunity	Yes	3664	(79.3%)
	Incomplete	336	(7.3%)
	No	329	(7.1%)
	Not determined / missing	291	(6.3%)
STI in the 6 months prior to PrEP start	Chlamydia	231	(5.0%)
	Gonorrhea	261	(5.6%)
	Syphilis	234	(5.1%)
	Multiple STI before PrEP start	196	(4.2%)
	No STI in the 6 months prior to PrEP start	2777	(60.1%)
	Unknown / missing	921	(19.9%)

Forty-three of the 47 centers, who responded to the additional center survey, reported caring for a total of 27 552 HIV-positive patients and 22 366 PrEP users.

PrEP use

Duration of PrEP use within the period of observation (September 2019-December 2020) were 5132 py; median duration was 451 days (IQR 357-488). More than one-half of PrEP users had started PrEP prior to September 2019 (n=2466, 53.4%). Taking this into consideration, PrEP duration was 7353 py with a median of 500 days (IQR 388-766). Intermittent, on-demand PrEP was documented for 18.9%. The average number of days of PrEP as prescribed divided by the number of days on PrEP was 0.85 (SD = 0.23). Almost one-third (n=1460, 31.6%) had a calculated PrEP pill coverage of less than 85 percent.

Ten percent of PrEP users had at least one PrEP interruption with a median duration of 93 days (IQR 58-148) and with the first interruption following at a median of 238 days (IQR 119-458) after PrEP start. PrEP discontinuations were documented for 13.2% after a median time of 275 days (IQR 142-478). More than one-third of the reasons for PrEP discontinuation or interruption were SARS-CoV-2 related (38.2%); also, PrEP interruptions were highest in March and April 2020 (49.5%), at the time of the first lock-down (figure 2, 3). Adverse reactions were reported by 3.3% as the reason for PrEP discontinuation or interruption (figure 3).

Twelve percent (n=555) did not have any event related to PrEP use (testing, diagnosis, treatment of STI, HIV, Hepatitis, or PrEP prescriptions) for at least two time intervals before their last event, 84.5% (n=469) of whom did not indicate PrEP discontinuation or interruption.

HIV

During the observation period, four persons became diagnosed with HIV-infection while on PrEP (MSM, age 26-33), accounting for 0.087% and an incidence rate of 0.078/100py (95% CI 0.029-0.208). HIV-infections were diagnosed on day 32, 167, 270 and 295 after start of study observation, which corresponds to day 32, 167, 595 and 598 after PrEP start. For two individuals PrEP on demand was documented, for the other two continuous PrEP. The reason for infection in two cases was reported to be suboptimal adherence. In the third case, calculated PrEP pill coverage was 0.6 and resistance to FTC was observed. The fourth person, diagnosed on day 32 after PrEP initiation, reported condomless rectal intercourse a few days prior to PrEP start.

Three of these patients were also diagnosed with other STIs. Two of the individuals had presented with a Syphilis infection in the previous six months before PrEP start and three had other STIs during the observation period (Table 2).

Table 2
Description of persons with HIV-infections

Age	PrEP indication	PrEP use	Quotient Pills/days PrEP	PrEP start	PrEP interruption	Last HIV negative test	HIV positive test	Days from PrEP start to HIV infection	Days from observation start to HIV infection	Reasons for HIV infection	HIV resis
26	MSM	On demand	0.71	05.12.2019	No	11.03.2020	20.05.2020	167	167	PrEP on demand with poor adherence	No
27	MSM	Continuous	1.82	06.01.2020	No	17.12.2019	07.02.2020	32	32	HIV risk before PrEP start	No
33	MSM	On demand	0.75	01.02.2019	Yes 01.09.2019 – 03.02.2020	27.01.2020	18.09.2020	595	270	PrEP on demand with poor adherence	Other resis not TDF/ asso
33	MSM	Continuous	0.60	02.11.2018	Nein	23.01.2020	22.06.2020	598	295	Not documented	FTC resis (M1E

The 43 centers, which responded to the separate study center survey and cared for a total of 22 366 PrEP users, reported 20 new HIV-infections on PrEP (0.089%).

STI – Chlamydia, Gonorrhea, Syphilis

Twenty percent of the study population were reported to have had an STI in the six months prior to PrEP start. At baseline, prevalence of STIs were 7.01% (95% CI 6.05-8.09) for Chlamydia, 6.62% (95% CI 5.68-7.66) for Gonorrhea and 3.63% (95% CI 2.93-4.44) for Syphilis.

Incidence rates during PrEP use in the observation period were 21.55/100py (95% CI 20.24-22.93) for Chlamydia, 23.73/100py (95% CI 22.35-25.17) for Gonorrhea and 10.08/100py (95% CI 9.18-11.03) for Syphilis. The total incidence rate of any STI in our cohort was 55.36/100py (95% CI 53.24- 57.54). The total incidence of any STI significantly decreased over time. Incidence rates over time are shown in figure 4 and Table 3 and were highest for all three infections in the first time interval (September-December 2019). While the lowest incidence rates were seen in the second quarter of 2020 for both Chlamydia and Gonorrhea, it was lowest for Syphilis in the third quarter. A rise in the incidence of Gonorrhea and Syphilis was again seen towards the fourth quarter of 2020 despite fewer tests. Overall, a significant reduction of 34.8% was found for Chlamydia and of 26.1% for Gonorrhea over the course of the observation period, as well as a reduction of 38.4% for Syphilis from the first time interval through the third quarter of 2020. The total incidence of any STI showed a significant reduction of 29.6% over the course of the observation period.

Table 3
Incidence of STI infections on PrEP over time from September 2019 to December 2020

	09/2019-12/2019	2020q1	2020q2	2020q3	2020q4	Overall
Persons	1932	3842	4327	4226	4099	4620
Person years (PY) at risk	592.25	931.34	1054.07	1048.84	1017.91	4644.41
Positive results Chlamydia	166	220	191	238	186	1101
Chlamydia incidence rate	28.03/100py	23.62/100py	18.12/100py	22.69/100py	18.27/100py	21.55/100py
95% CI	(24.07-32.63)	(20.7-26.96)	(15.72-20.88)	(19.98-25.77)	(15.83-21.1)	(20.24-22.93)
Positive results Gonorrhea	185	257	198	227	235	1102
Gonorrhea incidence rate	31.24/100py	27.59/100py	18.78/100py	21.64/100py	23.09/100py	23.73/100py
95% CI	(27.04-36.08)	(24.42-31.18)	(16.34-21.59)	(19.00-24.65)	(20.32-26.24)	(22.35-25.17)
Positive results Syphilis	76	100	113	83	96	468
Syphilis incidence rate	12.83/100py	10.74/100py	10.72/100py	7.91/100py	9.43/100py	10.08/100py
95% CI	(10.25-16.07)	(8.83-13.06)	(8.92-12.89)	(6.38-9.81)	(7.72-11.52)	(9.18-11.03)
Positive results any STI	427	577	502	548	517	2571
Any STI incidence rate	72.10/100py	61.95/100py	47.62/100py	52.25/100py	50.79/100py	55.36/100py
95% CI	(65.42-79.27)	(57.00-67.22)	(43.55-51.98)	(47.96-56.81)	(46.51-55.36)	(53.24-57.54)

Over one-third of the study participants (n=1728, 37.4%) were reported to have had at least one STI in the observation period. During the study, 1203 tests for Chlamydia were positive in 21.0% (971/4620). For Gonorrhea and Syphilis these were 1324 positive tests in 21.4% (987/4620) and 602 positive tests in 8.9% (409/4620) respectively. More than one infection with Chlamydia, Gonorrhea and Syphilis were reported for 20.0% (194/971 persons), 24.1% (238/987 persons) and 18.3% (75/409 persons) respectively. Sixty-seven individuals (1.5%) had infections with all three pathogens.

Syphilis was tested for more frequently than Chlamydia/Gonorrhea (18 598 vs. 12 789 tests). (Fig. 2) The median number of tests per individual was three for Chlamydia/Gonorrhea (IQR 2-4, range 0-20) and four for Syphilis (IQR 3-5, range 0-20). More than three-quarters had at least three tests for Syphilis (n=3630, 78.6%), while 43.6% (n=2016) had at least three tests for Chlamydia/Gonorrhea. No testing for Chlamydia/Gonorrhea was documented for 22.6% (n=1046), while no testing for Syphilis was reported for 1.6% (n=76). During the observation period, the lowest number of tests for Chlamydia and Gonorrhea were found in the second and fourth quarter of 2020 (n=2186 and n=2171, respectively) and for Syphilis in the fourth quarter of 2020 (n=3183).

The positivity rate remained relatively constant with a mean of 9.2%, 9.9% and 3.0% for Chlamydia, Gonorrhea and Syphilis respectively (Fig. 2). While 65.5% of Syphilis diagnosis were detected by screening of asymptomatic individuals, these were 55.6% for Chlamydia and 50.1% for Gonorrhea. The proportion of screening tests of asymptomatic individuals in view of all tests was 84.1% (10 759/12 789) for Chlamydia/Gonorrhea and 94.9% (17 645/18 598) for Syphilis.

The multivariable analysis of risk factors associated with Chlamydia/Gonorrhea infections among MSM showed a significantly higher risk for persons 16 to 29 years of age (OR 1.23, 95% CI 1.06-1.42), with PrEP start before statutory health insurance coverage (OR 1.24, 95% CI 1.07-1.44), with an STI history in the six months before PrEP start (OR 1.49, 95% CI 1.32-1.68) or an unknown STI history (OR 1.34, 95% CI 1.17-1.54), and with a higher number of symptomatic induced tests for Chlamydia/Gonorrhea (OR 1.87, 95% CI 1.77-1.98). A significantly lower risk for infections with Chlamydia/Gonorrhea was found for persons 40 to 49 years of age (OR 0.74, 95% CI 0.66-0.85) or 50 to 59 years of age (OR 0.60, 95% CI 0.50-0.72), with on-demand PrEP use (OR 0.78, 95% CI 0.67-0.91), and with a higher number of asymptomatic tests for Chlamydia/Gonorrhea (OR 0.91, 95% CI 0.87-0.95). (Supplement Table 1)

The analysis of risk factors associated with infections among MSM with Syphilis showed a significantly higher risk for persons 50 to 59 years of age (OR 1.53, 95% CI 1.18-1.97), with an STI history in the six months before PrEP start (OR 2.60, 95% CI 2.13-3.17), and with a higher number of symptomatic induced tests for Syphilis (OR 1.92, 95% CI 1.74-2.13). (Supplement Table 2)

Hepatitis

In 3358 (72.7%) of individuals Hepatitis A vaccination was reported, and 3664 (79.3%) had protection through antibodies against hepatitis B.

During the period of observation, two infections with hepatitis B were diagnosed on days 197 and 229 after start of observation, accounting for 0.043% and an incidence rate of 0.04/100py (95% CI 0.01-0.16). Thirteen cases of hepatitis C were found at a median of 267 days (IQR 137-353) after start of observation in the study, and accounting for 0.28%, a positivity rate of 0.30% (4273 tests) and an incidence rate of 0.25/100py (95% CI 0.15-0.44).

Additionally, one case of each, hepatitis A and B infection, and hepatitis C were diagnosed prior to or at the start of observation in the study (on days -7, 0, and -32 respectively).

Discussion

To our knowledge this is the first comprehensive description and analysis of real-life PrEP use and monitoring in the largest available population of PrEP users in Germany. The cohort of PrEP users studied was predominantly male, had MSM as an indication for PrEP and was on average under 50 years of age.

PrEP was found to be extremely effective in the prevention of HIV-infection in this routine clinical setting. The observed incidence rate of 0.078/100py is comparable with and even lower than in other studies. The early iPrEX OLE study reported an HIV incidence of 1.83/100py and a strong protective effect with adequate drug levels. No HIV-infection occurred in persons whose drug levels indicated an intake of four or more tablets per week (3). More recently, the PROUD study found an incidence of 1.2/100py, the DISCOVER study an incidence of 0.34/100py in the TDF/FTC group and the IPERGAY study reported an incidence of 0.91/100py with on-demand TDF/FTC (12–14). HIV-incidence among PrEP users in implementation projects were closer to our findings with 0.16/100py in New South Wales (EPIC-NSW) and 0.13/100py in England (PrEP Impact Trial) (15, 16). Differences in study populations and settings may partly explain differences in HIV-incidence. In addition, our results are certainly influenced by the SARS-CoV-2 pandemic and the associated contact restrictions. However, a considerable rate of other sexually transmitted infections, is proof that sexual contacts eventually took place during lockdown periods.

We found PrEP failure to be primarily linked to suboptimal adherence, which has been reported to be strongly correlated with efficacy (5, 17). In our cohort, four persons were diagnosed with HIV while on PrEP. The person diagnosed on day 32 after PrEP initiation reported condomless rectal intercourse few days prior PrEP start and very likely was infected with HIV at baseline. In further two persons, acquisition of HIV-infection was clearly linked to nonadherence. In one person failing on PrEP despite self-declared optimal adherence, resistance to FTC was documented. Yet, PrEP pill coverage for this person was calculated to be only 60%. And there were five months between the last negative and the first reactive HIV test. It therefore remains unclear whether this mutation was transmitted or selected for after transmission. Resistance to FTC is rare but well documented in persons with PrEP failure (5). In addition, the presence of sexually transmitted infections may have facilitated HIV transmission in these persons (18).

The cohort of PrEP users studied was largely male, 99% MSM and 83% under the age of 50, which is similar to that in other implementation studies (15, 16). In Germany, PrEP uptake appears to be minimal in risk groups outside of the MSM community. Making PrEP available by eliminating barriers and increasing access for people at risk requires further attention. This is supported by discussions with the community advisory board that have taken place within the scope of the EvE-PrEP project. The SARS-CoV-2 pandemic has further contributed to a reduced focus on prophylaxis especially in non-MSM groups (19).

PrEP use was most commonly prescribed for daily intake, with on-demand PrEP use reported by less than one quarter. However, calculated PrEP pill coverage indicated slightly higher on-demand use. PrEP interruptions and discontinuations were reported for ten and thirteen percent. Since twelve percent of PrEP users did not have any event related to PrEP use in the last two time periods of observation, possible interruption or discontinuation may not have been reported. The actual rate may therefore be higher up to around 20%. Approximately one-half of the PrEP interruptions occurred in March and April 2020 at the time of the first lock-down, and the reasons for PrEP discontinuations or interruptions were mainly SARS-CoV-2 related. Adverse reactions played only a minimal role, as seen in other studies (5, 12).

One major concern of PrEP availability is the potential for increased sexual risk taking and hence for sexually transmitted infections. At baseline twenty percent of our study population had a history of an STI in the previous six months which is associated with an increased risk of HIV infection (20). During the observation period 37% of the study participants were reported to have had at least one STI with a total incidence of any STI of 55.4/100py, indicating that these persons were sexually very active and that PrEP was prescribed to persons at risk (20, 21).

The observed incidences of STIs vary among studies and range from 72.2/100py (11) to 105.4/100py (16) depending on the population studied. In comparison, the incidence rates of STIs in our study were lower than in other international studies (7, 11). While some evaluations showed an increase of STI infection rates during PrEP use over time (22) we found a significant decrease. This decrease is very likely in part attributable to the SARS-CoV-2 pandemic and the measures taken to control it. Though the health counseling and awareness that is part of PrEP care may have also played a role.

The SARS-CoV-2 pandemic had a drastic influence on social behavior and sexuality. Yet sexual contacts in private settings took place with not necessarily lower risk potential. Sentis et al. found a 56 percent reduction in STIs during the March/April lockdown in Spain (23). It was concluded that the decline probably was due to the effect of a combination of factors including change in sexual behavior as well as decreased availability of resources and decreased use of health care (23).

Interestingly, rates over time differ between STIs. Infections with Chlamydia decreased with the lockdowns in the second and fourth quarters of 2020 and increased with social opening in the third quarter. After the initial decrease, infections with Gonorrhea, on the other hand, show a steady increase in both the third and the fourth quarters. Infections with Syphilis differ again, with their nadir in the third quarter, likely reflecting its longer incubation time (24, 25), followed by slight rise in the fourth quarter of 2020. The incidence of Syphilis infections was slightly higher when compared to other studies (7, 16).

When evaluating infection rates, it is important to consider testing rates. Testing for Chlamydia/Gonorrhea decreased in the second and fourth quarters, which may reflect the pandemic lockdowns. Other investigators have reported decreased testing for other infections, reduced use of health care as well as a marked reduction of spread of communicable diseases, including STI and HIV, in times of social lockdown (26, 27). In general, a drastic decline of notifications for most infectious diseases and pathogens in Germany was observed (28). Of the study centers, 76% reported a decrease of requests for PrEP during the first lockdown of the pandemic (19). Syphilis testing was higher throughout and decreased over the course of 2020. Although numbers of tests differed, the positivity rates remained relatively constant. While almost one-half of Chlamydia and Gonorrhea infections were a result of screening of asymptomatic persons, this was the case for two-thirds of Syphilis infections. The high rate of STIs found solely by screening asymptomatic MSM highlights its importance in the prevention of transmission. The lower testing numbers for Chlamydia/Gonorrhea appear to reflect the differing approaches taken by physicians and the controversies in Germany surrounding asymptomatic testing (29, 30).

The significantly higher risk of infection with Chlamydia/Gonorrhea for MSM aged 16 to 29 years and the significantly lower risk for MSM aged 40 to 59 years when compared to 30 to 39 years may reflect higher sexual activity and more partners in younger age groups. Unexpectedly, age 50 to 59 years was associated with an increased risk for syphilis. This finding is not supported by the national mandatory syphilis reports, which show the highest incidence for men between 30 to 39 years of age (31). Further analysis in terms of study center location indicated that there may be an interrelated infection pattern that possibly explains this discrepancy.

A higher risk for Chlamydia/Gonorrhea was found in MSM with PrEP start before its coverage by health care in September 2019. It likely reflects these individuals' involvement in the sexually active MSM community. In addition, this indicates persistent HIV risk behavior, which goes along with infection risks of other STIs. The lower risk for Chlamydia/Gonorrhea seen with on-demand PrEP use, on the other hand, may in turn reflect less frequent high-risk sexual contacts.

As expected, symptom triggered testing and a history of STI was associated with a higher risk for infections with Chlamydia/Gonorrhea and Syphilis. The latter supports the importance of a comprehensive anamnestic before PrEP initiation.

We found a high baseline protection against hepatitis A and B in approximately three-quarters of the cohort. Of note, immunity against hepatitis A may be in part self-reported and the actual percentage therefore lower. Antibodies against hepatitis B on the other hand should routinely be determined prior to commencing PrEP and every six months while on PrEP due to the interaction between tenofovir and hepatitis B (32). Accordingly, no infection with hepatitis A and only two with hepatitis B were diagnosed within the course of the study. However, thirteen cases of hepatitis C occurred, reflecting an ongoing epidemic of sexually transmitted hepatitis C among MSM, which in the past was almost exclusively seen among HIV infected MSM (33). Additionally, at screening before PrEP initiation one case of each hepatitis A, B, and C were detected underlining the importance of a medically guided PrEP start.

A limitation of this study is its evaluation period of sixteen months. Also, the SARS-CoV-2 pandemic drastically affected social interaction and probably influenced the outcomes found in this study. Further investigation in a regular non-pandemic setting with a longer follow-up period would be valuable. Partner numbers or sexual behavior were not documented. Our population may not represent all PrEP-users in Germany, nor all PrEP prescribing centers. However, since PrEP care is provided mostly by HIV-specialty practices in Germany, we assume that we were able to obtain a representative sample of PrEP users and study centers. With limiting the number of PrEP users that could be documented within each center, bias in patient selection may have taken place; a randomized approach was encouraged to avoid selection bias.

Conclusions

In Germany HIV-PrEP with TDF/FTC is almost exclusively taken by MSM. We found a very low incidence of HIV-infection in this cohort of PrEP users. The main reason for PrEP failure was suboptimal adherence. We did not see an increase in infections with Chlamydia, Gonorrhea and Syphilis; in fact, we saw a partial decrease in their incidence rates, very likely in part attributable to the SARS-CoV-2 pandemic. Our results support the coverage of PrEP medication and care by statutory health insurance. Increased PrEP availability to people at risk for HIV infection through the elimination of barriers and improved access requires further attention. Further investigation and monitoring with a longer follow-up would be of value.

List Of Abbreviations

CI Confidence interval

Dagnä e.V. Deutsche Arbeitsgemeinschaft niedergelassener Ärzte in der Versorgung HIV-Infizierter e.V. (German)

DISCOVER Study to evaluate the safety and efficacy of emtricitabine and tenofovir alafenamide (F/TAF) fixed-dose combination once daily for pre-exposure prophylaxis in men and transgender women who have sex with men and are at risk of HIV-1 infection

EPIC-NSW Expanded PrEP implementation in communities in New South Wales

EvE-PrEP Evaluation der Einführung der HIV-Präexpositionsprophylaxe als Leistung der Gesetzlichen Krankenversicherung (German)

HIV Human immunodeficiency virus

IPEGAY Intervention préventive de l'exposition aux risques avec et pour les GAYs (French)

iPrEX OLE "Iniciativa Profilaxis Pre-Exposición" (Spanish), open label extension

IQR Interquartile range

MSM Men who have sex with men

NEPOS National Evaluation of PrEP Outcomes and STIs

OR Odds Ratio

PrEP Pre-exposure prophylaxis

PROUD Pre-exposure option for reducing HIV in the United Kingdom

py Person years

RKI Robert Koch Institute

SARS-CoV-2 Severe Acute Respiratory Syndrome Coronavirus-2

STI Sexually transmitted infection

TDF/FTC Tenofovir disoproxil fumarate and emtricitabine

Declarations

Ethics approval and consent to participate

All patient data collected in NEPOS were generated during routine care. The data collected were anonymous. No direct patient survey or sampling took place within NEPOS. No human samples were collected and sent to the RKI. The Ethics Committee of the Berlin Chamber of Physicians reviewed the project and waived the need for ethical approval or informed consent, as it involves only retrospective anonymous data (Eth-KB 03/20). We confirm that all methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to data protection and confidentiality but are available from the corresponding author on reasonable request.

Competing interests

DS, MF, BB, VB, TS, MB, RR, KS, and NH declare that they have no competing interests. CK is small shareholder in companies manufacturing antiretroviral drugs. SS has received honoraria for lectures, conference sponsorship and participation on advisory boards from Abbvie, Gilead, Janssen, GSK, MSD, ViiV Healthcare, Theratechnologies. SVS has received honoraria and study compensation from companies developing and marketing antiretroviral drugs and is shareholder of various pharmaceutical companies including ones developing and marketing antiretroviral drugs.

Funding

The PrEP evaluation (EvE-PrEP) was funded by the Federal Ministry of Health, Germany. We acknowledge the financial support of the German Federal Ministry of Health. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Authors' contributions

DS was responsible for the study design, performed the data analysis and statistical analysis, interpreted the data and drafted the manuscript. CK contributed to the conception of the study and interpretation of the data and was responsible for the data management. KS, RR and NH contributed to the conception and coordination of the study and interpretation of the data and to draft the manuscript. MF and TS supported the management and coordination of the study and contributed to improving the data quality and coverage. SS, SVS, MB are site principal investigators, contributed data and supported the interpretation of the data. VB and BB supported the management and coordination of the study and the overall study design and analysis approach. All authors participated in the critical discussion of the results, and all read and approved the final manuscript.

Acknowledgements

The authors are grateful to the PrEP users and to all collaborative NEPOS centers for the data collection and study management in the centers. The authors would like to thank Andrea Sailer for her assistance in the preparation of figure 1 and Matthias an der Heiden for his support with the logistic regression analyses. We thank all cooperating partners in EvE-PrEP.

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Figures



Study centers N = 47

Figure 1

Distribution of participating study centers in Germany

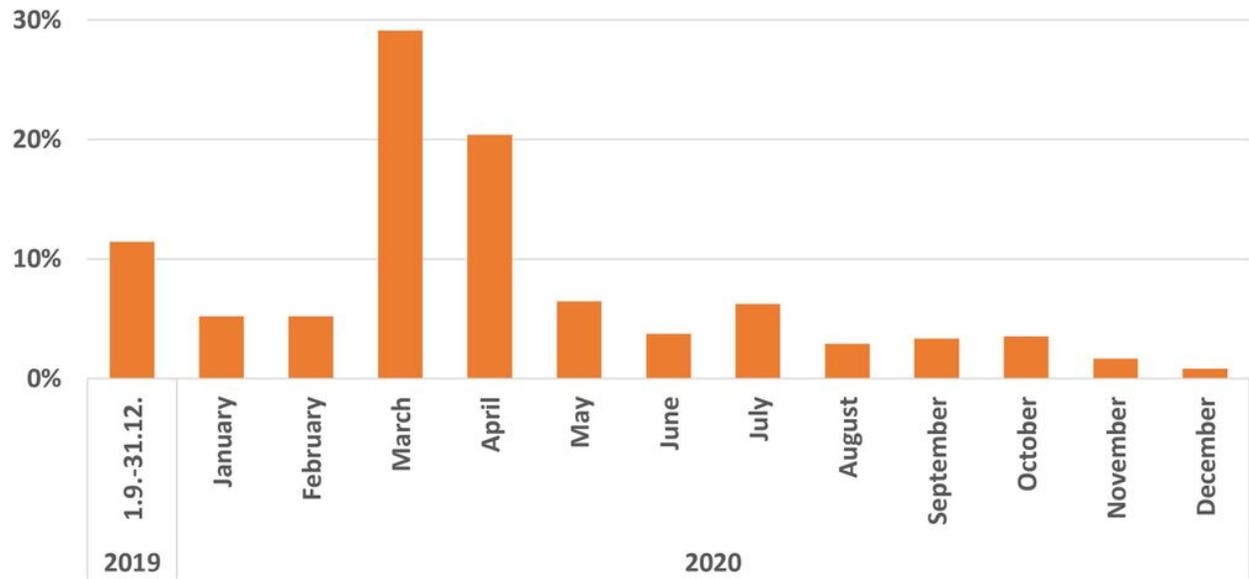
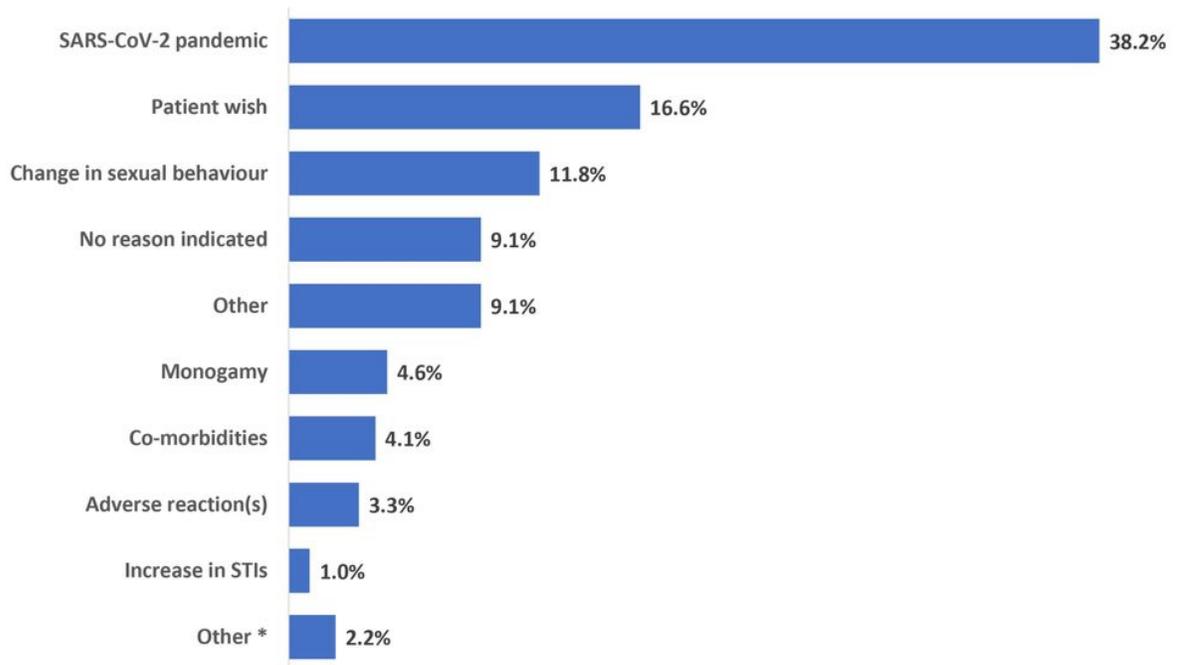


Figure 2

PrEP interruptions over time from September 2019 to December 2020



* Other (included time consuming, HIV infection, medical interaction, costs, doubt of effectiveness)

Figure 3

Primary reasons for discontinuing or interrupting PrEP

905 reasons were documented for 725 individuals, combinations of reasons were categorized accordingly

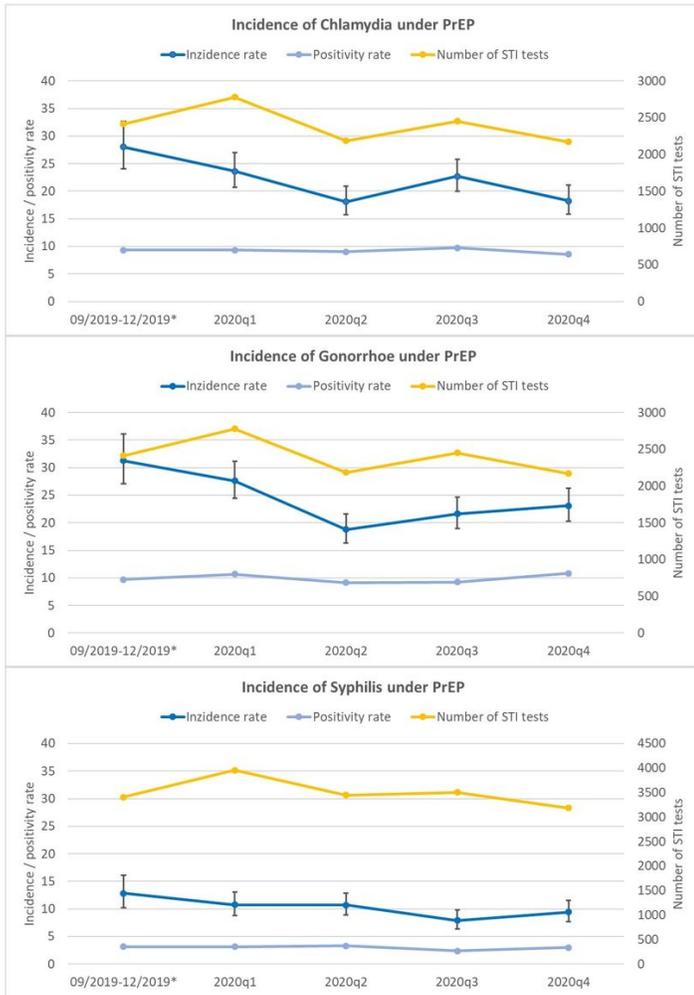


Figure 4

STI incidence rate, positivity rate and number of tests among German PrEP users over time from September 2019 to December 2020

* Number of tests were corrected for the time interval 09/2019-12/2019

Supplementary Files

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- [Supplementtable1table2.docx](#)