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Changes in the user profiles of HIV pre-exposure prophylaxis (PrEP) before and after PrEP reimbursement

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ABSTRACT

Background: In Germany, oral HIV pre-exposure prophylaxis (PrEP) was licensed in 2016. Health insurances have been covering the costs since 09/2019. This study compares the sociodemographic profiles of PrEP users before and after PrEP re-imbursement.
Methods: Participants were recruited in a cross-sectoral sexual health centre in Germany. baseline data were compared for 139 vs 138 individuals starting PrEP from 10/2017–12/2018 (pre-reimbursement cohort) and 09/2019–3/2020; respectively. The pre-reimbursement cohort was further analysed with respect to sexual behaviour and incident sexually transmitted infections (STIs).
Results: There were no significant differences in the sociodemographic characteristics between the two cohorts. Almost all PrEP users were men-who-have-sex-with-men (MSM). Before reimbursement, fewer individuals used PrEP on a daily base, and more had used PrEP prior to enrolment. During follow-up (pre-reimbursement cohort), the number of sexual and condomless intercourse partners increased, so did the proportion engaging in Chemsex. Incidences of infections with *C.trachomatis*, *N.gonorrhoeae*, *M.genitalium*, and *T.pallidum* were 45.2; 36.8; 30.1; and 9.2, respectively, per 100 person-years.
Conclusion: The goal to make PrEP available to a broader range of people with the covering of costs was only partially reached. Medically supervised use is important to detect and treat STIs.

Introduction

Oral Pre-Exposure prophylaxis (PrEP) is an HIV prevention strategy. In the United States, a combination of the HIV therapeutics tenofovir disoproxil fumarate and emtricitabine (TDF/FTC), was licensed for this purpose in 2012. The European Medicines Agency (EMA) approved PrEP for the European Union, including Germany, in 2016 [1,2]. The efficacy of this medication to prevent HIV infections is well documented [3–5]. However, at the time of approval, PrEP was not affordable for most users at a price of more than 800€ per month for daily use. Thus, PrEP users often purchased PrEP from other sources than German pharmacies like online suppliers or from abroad and informal purchase was often associated with failing to obtain regular medical check-ups including STI-testing [6–8]. In Germany since 10/2017, generics of PrEP have been available for 40–70€. After 09/2019 the costs of PrEP and regular screening interventions have been covered by health insurance for individuals at substantial HIV risk.

In this paper we compare the sociodemographic profiles of PrEP users before and after PrEP re-imbursement. Additionally, we longitudinally analysed sexual behaviour and incident sexually transmitted infections (STIs) in participants of the pre-reimbursement cohort. However, we expected that the barrier to use PrEP would be reduced after reimbursement in PrEP-users with lower grade of education and income in comparison with the participants of the

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pre-reimbursement cohort. Furthermore, we expected higher incidences of other STI than HIV during the study period.

Materials and methods

The study was conducted at `Walk In Ruhr` (WIR), a large sexual health centre in Bochum, Germany, which has started counselling and monitoring PrEP users in 10/2017. WIR is a model for cross-sectoral care and comprises the Interdisciplinary Immunological Outpatient Clinic, the Local Health Authority Bochum and non-government organisations such as AIDS Service Organization Bochum.

Participation in this monocentric, prospective study was offered to all PrEP users at WIR who were 18 years or older, at substantial risk for HIV infection and had an estimated glomerular filtration rate according to Modification of Diet in Renal Disease (MDRD)-formula > 80 ml/min (or > 60 ml/min and green light by a nephrologist). Exclusion criteria were infection with hepatitis B virus (HBV) and a poor knowledge of the German language. All participants provided written informed consent.

Between 10/2017 and 12/2018 169 PrEP users at WIR were offered to participate, 30 declined and 139 accepted (pre-reimbursement cohort). Between 9/2019 and 3/2020 138 PrEP users (137 MSM, one woman) were recruited to the reimbursement cohort. Only the participants of the pre-reimbursement cohort were observed for 13 months.

The observation period for all participants of the pre-reimbursement cohort was approximately 13 months (follow-ups at month 1, 4, 7 and 13). Participants were considered as lost to follow-up if they missed at least two consecutive follow ups or missed the last follow up with no chance to recall, or if they declined further participation. If participants missed follow ups because of pausing PrEP, they received regular recalls and had the possibility to continue when re-starting PrEP. The overall follow-up time was 119.5 person years.

Data collection

Questionnaires

At baseline, participants filled in a self-constructed 33-item questionnaire, which was used before in another study about the scientific accompaniment of WIR [9]. The questionnaire includes questions on origin, educational and occupational background, gender of sexual partners, previous use of PrEP or post-exposure prophylaxis (PEP), use of chemsex-drugs (gamma-hydroxy-butyric-acid/gamma-butyrolactone, cocaine, 'ecstasy', ketamine, or methamphetamine), inhaled alkyl nitrites ('poppers'), or inhibitors of phosphodiesterase-5 during sex in the previous six months. Also recorded were the self-reported numbers of male and female sexual partners and of condomless intercourse partners (open write-in field), sex with HIV-positive partners and transactional sex, all in the previous six months; and the type of PrEP-use (daily or intermittent/on demand) planned at baseline.

A 15-item follow up questionnaire was provided at month 7 and 13. This questionnaire included the same sexual behaviour questions and a question about possible deviations from the type of PrEP use.

Laboratory and clinical examinations

Laboratory examinations were conducted according to German clinical guidelines HIV RNA (only at baseline), 4th generation HIV antibody test, viral p24-antigen, creatinine, estimated creatinine-clearance according to Modification of Diet in Renal Disease-formula (MDRD-formula), phosphate, glucose, natrium, potassium, urinalysis, anti-HAV-IgG (Hepatitis A virus), anti-HBs (Hepatitis B-surface), anti-HBc (Hepatitis B-core), anti-HCV (Hepatitis C virus) or HCV RNA if anti-HCV positive, TPPA [Treponema pallidum particle agglutination assay], VDRL (Venereal Disease Research Laboratory) [1]. STI-testing was initially performed at baseline (STI which were detected at the uptake and 30 days before were counted) and next time at month 4. Infections with *Neisseria gonorrhoeae* (*NG*), *Chlamydia trachomatis* (*CT*), *Mycoplasma genitalium* (*MG*) and *Trichomonas vaginalis* (*TV*) were tested by self-collected oral and rectal swabs and first urine for Nucleic Acid Amplification Test (Cobas CT/NG, Roche Diagnostics, Mannheim, Germany; Cobas TV/MG, TIB Molbiol, Roche Diagnostics, Mannheim, Germany). All participants with incident infections with CT, NG, MG or TV received a test of cure (TOC) six weeks after diagnosis. Incident HCV-infection was defined by seroconversion of anti-HCV and or detection of HCV-RNA. Every treated TP infection was determined as incident syphilis. Furthermore, at each visit, we checked if the participants had a documented STI outside this study. Participants with no or insufficient antibodies against HAV or HBV were referred to vaccination. According to German guidelines, sufficient immune response was defined as anti-HAV-IgG > 20 U/l. Although, anti-HBs-IgG > 10 U/l is considered as sufficient protection against hepatitis B infection, participants with anti-HBs-IgG < 100 U/l were recommended to get a booster-vaccination. Thus, we chose a cut-off of anti-HBs-antibodies > 100 U/l to define adequate immune protection in our study.

Criteria for premature termination were a GFR < 60 ml/min, other medical reasons, or the client's will to drop out. The GFR of 3 participants decreased under 60 ml/min. After green light by a nephrologist the participants could continue with PrEP and the participation in the study.

Data evaluation

Data was pseudonymized using a six-digit code and evaluated as absolute and relative frequencies.

We used Chi-squared test and p-value to determine differences in socioeconomic characteristics across the two cohorts and in the pre-reimbursement cohort to determine changes over time in the proportion of participants engaging in chemsex. To detect significant changes in the numbers of sexual and condomless intercourse partners we used the Friedmann and Wilcoxon test. McNemar test was used to analyse connected samples paired according to the usage of condoms; also, we calculated adjusted odds ratios for condom use. The level of significance was determined at 5 %, for multiple tests corrected by the Holm-Bonferroni method. Finally, we calculated incidences of STIs and hepatitis C per 100 person-years.

Results

In the pre-reimbursement cohort, 104 out of 139 PrEP users participated until the end of the study. After the initial four weeks four participants paused PrEP, and ten participants were lost to follow-up, thus 125 participants in total completed the first follow up. At the end of the study, 17 participants were lost to follow up and 18 participants had paused PrEP at some point during follow-up. In the reimbursement cohort, 139 participants were enrolled.

Sociodemographic and -economic background of PrEP users

The median age of PrEP users in the pre-reimbursement cohort was 38 years (range 18–62 years) vs 34 years (18–66 years) in the reimbursement cohort. A proportion of 96.4 % vs 98.6 % identified as men *and* reported same-sex sexual contacts (only men or men and women) in the previous six months (Table 1).

No significant differences were found regarding the country of birth (x^2 = 0.0054, p = 0.9409), most of the participants were born in Germany (82.7 % vs 85.5 %). Most of the participants reported attending school for more than 12 years vs attending school less than

Table 1
Sociodemographic characteristics of PrEP users at baseline across both cohorts.

	Pre-reimbursement Cohort[a] (N = 139)	Reimbursement cohort[b] (N = 138)
Median Age	38 years	34 years
Gender of the participants		
Male	139 (100.0 %)	137 (99.3 %)
Female	0 (0.0 %)	1 (0.7 %)
Country of birth		
Germany	115 (82.7 %)	118 (85.5 %)
Abroad	19 (13.7 %)	19 (13.8 %)
Not answered	5 (3.6 %)	1 (0.7 %)
Gender of sexual partners		
Only men	126 (90.6 %)	128 (92.8 %)
Only women	1 (0.7 %)	0 (0.0 %)
Men and women	8 (5.8 %)	8 (5.8 %)
Not answered	4 (2.9 %)	2 (1.4 %)
Previous PrEP use		
Yes	27 (19.4 %)	15 (10.9 %)
No	108 (77.7 %)	122 (88.4 %)
Not answered	4 (2.9 %)	1 (0.7 %)
Previous PEP prescription		
Yes	34 (24.5 %)	11 (8.0 %)
No	102 (73.4 %)	126 (91.3 %)
Not answered	3 (2.2 %)	1 (0.7 %)
Intended regime of application		
Daily	107 (77.0 %)	125 (90.6 %)
Event-driven	25 (18.0 %)	12 (8.7 %)
Daily with longer pauses	2 (1.4 %)	0 (0.0 %)
Not answered	5 (3.6 %)	1 (0.7 %)
Number of years in primary and secondary education		
12 years or more	103 (74.1 %)	97 (70.3 %)
10–11 years	33 (23.7 %)	37 (26.8 %)
9 years or fewer	1 (0.7 %)	1 (0.7 %)
Not answered	2 (1.4 %)	3 (2.2 %)
Profession		
Employed, civil servant, self-employed	99 (71.2 %)	86 (62.3 %)
Retired	4 (2.9 %)	5 (3.6 %)
Apprenticeship, studies, school	26 (19.7 %)	29 (21.0 %)
Unemployed	2 (1.4 %)	6 (4.3 %)
Other labor situation	5 (3.6 %)	0 (0.0 %)
Not answered	3 (2.2 %)	8 (5.8 %)

Abbreviations: PrEP: Pre-exposure prophylaxis; PEP: Post-exposure prophylaxis.
[a] Started PrEP between 10/2017 and 12/2018.
[b] Started PrEP between 9/2019 (after German health insurances began covering the costs of PrEP) and 3/2020.

12 years with no significant differences between the two cohorts (74.1% vs 70.3 %; x^2 = 0.3875, p = 0.5336).

Regarding to the current occupation, there also were no significant differences between the two cohorts (x^2 = 0.6965, p = 0.7059). Most of the participants were employed, civil servant or self-employed (71.2 % vs. 62.3 %).

Previous and planned PrEP use

The majority of participants in both cohorts opted for daily PrEP use (77 % vs 91 %; x^2 = 5.8732, p = 0.0154, Table 1). In the pre-reimbursement cohort, the proportion of participants who used PrEP daily increased to 81.7 % after 13 months. A proportion of 19 % vs 11 % reported prior PrEP use and 34 participants reported PrEP use prior to enrolment (x^2 = 4,2663, p = 0,0389). Previous use of post-exposure prophylaxis (PEP) was reported by 25 % vs 8 % (x^2 = 9,8065, p = 0,0017). Before initiating PrEP at WIR, use of PEP and informal use of PrEP was significantly higher than before reimbursement. Before their use of PrEP at WIR, 14 of 27 participants (51.9 %) in the pre-reimbursement cohort reported obtaining PrEP through pharmacies in Germany for 50 € per one-month package. Prior to study enrolment, 9 participants of the pre-reimbursement cohort vs 1 participant of the reimbursement cohort had purchased PrEP abroad, online (6 vs 0 participants), obtained it via friends (3 vs 1 participants), or used PEP as a form of PrEP (1 vs 2 participants).

The proportion of the participants of the pre-reimbursement cohort, who obtained PrEP through pharmacies in Germany increased to 96.8 % after the first four weeks of PrEP intitiation at WIR and was nearly stable during the following twelve months.

Sexual behaviour and substance use in the pre-reimbursement cohort

The participants had sex with a median of 6 partners in the previous 6 months (range 0–100 partners; not answered by 4 participants) at baseline (Fig. 1) and with a median of 10 partners at month 13 (range 0–100 partners; not answered by 35 participants). There was a significant increase in the numbers of sexual partners and condomless intercourse partners overall (p = 0.0217) especially when comparing baseline and month 7 (p = 0.0344). Comparing baseline with month 13 (p = 0.0592) and also comparing month 7 with month 13, there (p = 0.5566) was no significant increase in each period.

The median number of condomless intercourse partners increased significantly from 2 at baseline (range 0–100; not answered by 8 participants) to 6 (0–100; not answered by 35 participants) at month 13 (Fig. 1). The numbers of condomless intercourse partners increased significantly in the whole timeframe of the study and also when comparing the different parts of the study (Total: p ≤ 0.0001; baseline vs month 7, p ≤ 0.0001; baseline vs month 13, p ≤ 0.0001; month 7 vs month 13, p = 0.0332).

At baseline, 98 participants (74.8 %) reported condomless intercourse in the previous six months. This proportion increased to 91.8 % at month 7 %, and 94.2 % at month 13, respectively. Thus, there was a significant decrease in condom use overall (p = 0.006) and particularly when comparing baseline and month 13 (p = 0.013).

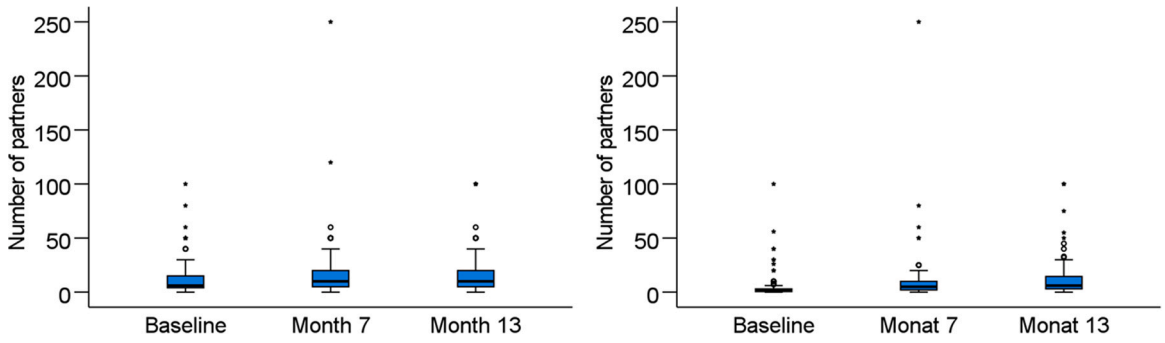

Fig. 1. Number of sexual partners in total (left) and without the use of condoms (right) in the last six months.

Table 2
Substance use among participants in context of sex.

	Baseline (N = 137)	Month 7 (N = 110)	Month 13 (N = 104)	Baseline vs. month 7		Baseline vs. month 13		Month 7 vs. month 13	
				Chi-square-test x^2	p-value	Chi-square-test x^2	p-value	Chi-square-test x^2	p-value
Alkyl nitrites	43.8 %	52.7 %	46.2 %	0.63	0.4287	0.133	0.7153	0.1488	0.700
Inhibitors of phosphodiesterase-5	20.4 %	26.4 %	25.0 %	0.57	0.4507	0.7077	0.4002	0.012	0.9128
Typical chemsex-drugs[a]	14.6 %	23.6 %	19.2 %	6.09	0.0136	5.57	0.0183	0.0014	0.9702
GHB/GBL	9.5 %	10.9 %	10.6 %	0.03	0.8729	0.078	0.780	0.0146	0.9038
Ecstasy	7.3 %	12.7 %	7.7 %	1.49	0.2222	0.0133	0.9082	1.035	0.309
Cocaine/Amphetamines	6.6 %	10.0 %	9.6 %	0.63	0.4265	0.7553	0.3848	0.009	0.9244
Ketamine	3.7 %	6.4 %	4.8 %	0.71	0.3992	0.1993	invalid	0.1259	0.7227
Methamphetamine	0.0 %	0.0 %	0.0 %	/	/	/	/	/	/

Abbreviations: PrEP: Pre-exposure prophylaxis; GHB: Gamma-Hydroxybutyric acid; GBL: Gamma-Butyrolactone.
[a] Typical chem sex-drugs including any of GHB/GBL, Ecstasy, Cocaine/Amphetamines, Ketamine, Methamphetamine.

The number of participants reporting transactional sex was constantly low. Six persons (4.4 %) sold sex and four persons (3.0 %) paid for sex before they started PrEP.

Alkyl nitrites and inhibitors of phosphodiesterase-5 were used by 43.8 % and 20.4 % of participants, respectively, at baseline (Table 2), without a clear trend over time. Typical chemsex-drugs including GHB/GBL, ecstasy, cocaine/amphetamines, ketamine and methamphetamine were used by 14.6 % of the participants at baseline compared to 23.6 % at month 7 % and 19.2 % at month 13. Thus, there was a small but significant increase in the overall use of chemsex-drugs at baseline compared with later visits (baseline vs month 7, p = 0.0136; baseline vs month 13: p = 0,0183), but no significant changes for any substance on its own.

HIV and STIs

No incident HIV infection was observed.

A total of 147 incident STIs (other than HIV) were observed in 66 of 139 participants within 13 months (Table 3). The total number of each STI and each follow-up are shown in Table 3. The incidence of infections with *CT* was 45.2 per 100 person-years, with *NG* 36.8 per 100 person-years, with *MG* 30.1 per 100 person-years, with *Treponema pallidum* 9.2 per 100 person-years, resulting in an overall incidence of 55.2 per 100 person years. We detected no infection with *TV* during the course of the study.

Also, two new infections with HCV were diagnosed simultaneously in month 4, resulting in an incidence of 1.7 per 100 person-years over the whole study period.

80 participants (57.6 %) demonstrated adequate immune protection against HAV and 65 participants (46.8 %) against HBV (using the cut-off of 100 U/l) prior to the initiation of PrEP. These proportions increased to 92.3 % for HAV respectively 82.7% for HBV at the end of the study period.

Discussion

In our study centre, daily use of PrEP increased with the re-imbursement of costs, but the observed changes in the socio-demographic profiles of PrEP users before and after re-imbursement were smaller than expected. However, we expected that the participants of the pre-reimbursement cohort would have a higher grade of education and that the rate of unemployment would be lower in comparison to the reimbursement cohort regarding to the cost of PrEP.

Over time, in the pre-reimbursement cohort, the numbers of sexual partners and condomless intercourse partners increased substantially among participants, so did the proportion of men engaging in Chemsex. This might explain the very high incidence of bacterial STIs found in our study.

Since enrolment into the pre-reimbursement cohort started (10/2017) after PrEP was licensed (2016) but before it was covered by German health insurances (09/2019), participants had to pay about 50€ per month for PrEP. The high educational background and good employment status of the PrEP users in our study reflect that they were able to financially afford PrEP. The median age of these PrEP users was 38 years, reflecting previously performed PrEP acceptance studies in Germany [10]. The sociodemographic data of PrEP users in our centre was comparable to that reported by Reynier et al., 2018 study of PrEP users in Belgium, with 74.1 % vs 77.5 % with 12 years or more spent in primary or secondary education and 77.7 % vs 78.5 % reporting current employment [11].

In the reimbursement cohort there was a trend towards younger age without a significant difference regarding to the years spent in secondary education and the profession. The percentage of migrant PrEP users was comparably low in both cohorts, hence we believe that many migrants (28 % of the population in Bochum) were unaware of PrEP, had doubts about its efficacy, or did not know that costs of PrEP were meanwhile covered by statutory health insurance.

The percentage of persons who used PrEP before they started prescription at WIR in the reimbursement cohort was significantly lower than in the pre-reimbursement cohort. Also, purchasing PrEP

Table 3
Total number of incident STIs.

Number of STIs (%)	Baseline (N = 139)	Month 4 (N = 120)	Month 7 (N = 110)	Month 10 (N = 104)	Month 13 (N = 104)	Overall follow-up time of 13 months
Chlamydia trachomatis	8	15	14	15	10	54
Neisseria gonorrhoeae	10	13	8	15	8	44
Mycoplasma genitalium	7	10	9	10	7	36
Treponema pallidum	4	3	1	3	4	11
Hepatitis C	2	2	0	0	0	2
Total number of STIs for each Follow-up	/	43[a]	32	43	29	147

Abbreviations: **STI**: Sexually transmitted infection.
[a] Each participant can have a STI several times per follow up; each STI was counted.

from friends or abroad decreased in comparison with pre-reimbursement. Thus, we suggest that the covering of costs has a reducing effect on the informal acquisition of PrEP.

The proportion of participants who used PrEP daily was significantly lower in the pre-reimbursement cohort and moderately increased after 13 months. Saving money could have been a motive for not using PrEP on a daily basis. The percentage of participants in the pre-reimbursement cohort who obtained PrEP through German pharmacies for 50€ per one-month package increased as expected from 51.9 % to 96.8 % after the first 4 weeks of PrEP initiation at WIR. Medically supervised use and decreased dependence on foreign imported PrEP was achieved.

Both the number of sexual as well as the number of condomless intercourse partners significantly increased during the course of PrEP use in our study. Brooks et al. had earlier made a similar observation wherein 64 % of the participants reported that their sexual behaviour will probably change (more partners, less condom use) after starting PrEP [12]. In comparison to our study, an US study suggested that the use of condoms decreases significantly with increased PrEP use [13] while an Australian study suggested that the use of condoms was constant among PrEP users [14].

Our study confirms that use of alkyl nitrites ('poppers') and inhibitors of phosphodiesterase-5 among PrEP users in Germany remains relatively unchanged by time of PrEP use. Only the use of the before-mentioned chemsex-drugs increased significantly. In the UK-based PROUD study, the proportion of men using typical chemsex drugs was more than double as high [5], confirming previous studies that highlighted large variation in substance use across European cities [15].

Consistent with other studies on effectiveness of PrEP [3–5], no infection with HIV was detected in our study. A total number of 147 incident STIs in 66 participants within 13 months indicated a high rate of infections (most frequently *CT*, *NG* and in third place *MG*) during the course of PrEP use and was observed to be concomitant with an increased number of sexual partners and a decreased use of condoms. A high incidence of STIs in context with PrEP use has also been reported in similar groups by Traeger or Nguyen [16,17]. Traeger et al. observed a higher incidence of STIs among PrEP users due to higher number of anal sex partners and group sex but did not observe an association with the use of condoms. Consistent with our observation, CT was the most frequently detected pathogen among PrEP users in this study [16] whereas MG was more often detected in a study of Jansen et al. [18]. Both, the study of Traeger and the study of Jansen detected a higher incidence of STIs in PrEP-users after initiation of PrEP than before. Also, STIs incidence was much higher in PrEP-users than in MSM without PrEP-use. In the Swiss STAR trial, although restricting to men with at least 3 partners in the previous 12 months, incidence with MG, CT, NG, and TP were in comparison with the results of our study 7, 5, 2.5, 2.2 times lower [19]. Low TV incidences might be a German phenomenon. Thus, the incidence of TV was low in our study as well as in the German MSM Screening study [18]. The incidence of HCV-infections in our cohort was comparatively high with 1.7 per 100 person-years. The two cases might have been connected, and based on sexual history-taking, intra-cavernous injection was assumed to be the most likely way of HCV transmission.

In addition, the current study also demonstrates the importance of testing the status of protection through immunisation for hepatitis A and B.

We were able to increase the percentage of persons with adequate immune protection (s. materials and methods) against HAV (57.6–92.3 %) and HBV (46.8–82.7 %) during PrEP care at the WIR center.

Strengths and limitations

We systematically performed a test of cure (TOC) on almost all infected participants This allows us to determine all infections as truly incident STIs, which is of particular importance for Mycoplasma genitalium that is likely to persist due to high levels of antimicrobial resistance.

This study has several limitations, mainly the relative low number of participants. The study was mono-centric, so it is unclear to what extent our results can be extrapolated to MSM living in larger German cities. Our questionnaire did not include questions on group sex, or questions specific to HCV infection, so we relied on patient records and sexual history-taking to conclude that it was transmitted via needle-sharing in a sexual context.

In the follow-ups we observed a determined period of 6 months regarding to the incidence of STI. We missed to determine a comparable period for incident STI before start of PrEP. Thus, a comparison of the baseline data with the data of the follow-ups was not systematically possible.

Conclusion

Prior to re-imbursement of the costs, PrEP in our centre reached MSM at substantial risk for HIV, and with high educational background.

With the covering of costs, PrEP may be more accessible for a broader range of people and could lead to a more regular use of PrEP. Follow-up is important to detect STIs, especially in view of a decreased use of condoms and a higher number of partners.

Conflict of Interest

The authors whose names are listed on the title page certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non- financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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