What are the characteristics of, and clinical outcomes in men-who-have-sex-with-men prescribed HIV post-exposure prophylaxis following sexual exposure (PEPSE) at sexual health clinics in England?

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ABSTRACT

Objectives

To explore the risk factors for, and clinical outcomes in men-who-have-sex-with-men (MSM) prescribed HIV post-exposure prophylaxis following sexual exposure (PEPSE) at sexual health clinics (SHCs) in England.

Methods

National sexually transmitted infection (STI) surveillance data were extracted from the genitourinary medicine clinic activity dataset (GUMCADv2) for 2011-2014. Quarterly and annual trends in the number of episodes where PEPSE was prescribed were analysed by gender and sexual risk. Risk factors associated with being prescribed PEPSE among MSM attendees were explored using univariable and multivariable logistic regression. Subsequent HIV acquisition from 4 months after initiating PEPSE was assessed using multivariable Cox proportional hazards models, stratified by clinical risk profiles.

Results

During 2011-2014, there were 24,004 episodes where PEPSE was prescribed at SHCs, of which 69% were to MSM. The number of episodes where PEPSE was prescribed to MSM increased from 2,383 in 2011 to 5,944 in 2014, and from 1,384 to 2,226 for heterosexual men and women. 15% of MSM attendees received two or more courses of PEPSE. Compared to MSM attendees not prescribed PEPSE, MSM prescribed PEPSE were significantly more likely to have been diagnosed with a bacterial STI in the previous 12 months [aOR(95% CI) – gonorrhoea: 11.6(10.5-12.8); chlamydia: 5.02(4.46-5.67); syphilis: 2.25(1.73-2.93)], and were more likely to subsequently acquire HIV [aHR(95%CI) - single PEPSE course: 2.54(2.19-2.96); two or more PEPSE courses: aHR(95%CI) 4.80(3.69-6.25)]. The probability of HIV diagnosis was highest in MSM prescribed PEPSE who had also been diagnosed with a bacterial STI in the previous 12 months [aHR(95%CI): 6.61(5.19-8.42)].

Conclusions

47 MSM prescribed PEPSE are at high risk of subsequent HIV acquisition and our data show further risk
48 stratification by clinical and PEPSE prescribing history is possible, which might inform clinical practice
49 and HIV prevention initiatives in MSM.

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KEY MESSAGES

- PEPSE is a method to prevent HIV infection, but there are limited data on the surveillance and epidemiology of PEPSE prescribing at a national level.
- During 2011-2014, the number of episodes where PEPSE was prescribed increased markedly in MSM compared to heterosexual men and women.
- MSM prescribed PEPSE, and in particular those prescribed two or more courses, are at high risk of subsequent HIV infection.
- These data might support clinical risk assessment decisions, including about the need for PrEP as part of a multi-component HIV prevention package.

INTRODUCTION

Post-exposure prophylaxis following sexual exposure (PEPSE) is a potential method to prevent HIV infection. Current UK guidelines recommend that PEPSE, consisting of a 28-day course of antiretroviral therapy (Truvada (emtricitabine/tenofovir) and raltegravir) is offered to individuals who present within 72 hours of a defined risk exposure such as receptive unprotected anal intercourse (UAI) with a partner of unknown HIV status and from a known risk-group.[1] An HIV test is performed at baseline to rule out undiagnosed HIV infection, and a follow-up HIV test is performed 8-12 weeks post-exposure.[1]

Prospective randomised controlled trials (RCTs) to measure the efficacy of PEPSE are not ethically justifiable.[1] Consequently, there is a lack of evidence on the clinical effectiveness of PEPSE, and current UK guidelines draw on observational studies, animal studies, and an understanding of the biology of HIV transmission.[1] The guidelines also state that other HIV prevention strategies should be prioritised, such that PEPSE is considered only where these have failed.[1]

In the UK, men-who-have-sex-with-men (MSM) are the population most at-risk of acquiring HIV, accounting for over half (55%; 3,360) of all new HIV diagnoses reported in 2014. The number of HIV diagnoses annually in MSM has shown a steadily rising trend over the past decade, which can be explained by increases in HIV testing as well as high levels of on-going HIV transmission.[2,3]

We analysed PEPSE prescribing in sexual health clinics (SHCs) in England using national surveillance data to understand better the role of PEPSE in HIV prevention, including any future pre-exposure prophylaxis (PrEP) policy, and to inform clinical decision making and resource allocation. We have described recent trends in PEPSE prescribing in SHCs and explored the risk factors for, and subsequent HIV diagnoses in MSM attendees prescribed PEPSE.

METHODS

Data source

Data were extracted from the genitourinary medicine clinic activity dataset (GUMCADv2), a patient-level dataset containing information on sexually transmitted infection (STI) diagnoses and services provided by all genitourinary medicine (GUM) and integrated GUM/sexual & reproductive health services in England (referred to as SHCs). Clinical data are reported using national Sexual Health and HIV Activity Property Type (SHHAPT) codes and each attendance includes information on patient demographics (gender, age, sexual orientation, self-reported ethnicity and country of birth) and area of residence.[4] The national SHHAPT code for PEPSE ("PEPS") was introduced on 1st January 2011. Attendances by the same individual can be linked within SHCs (but not between clinics), enabling the identification of repeat visits and subsequent clinical diagnoses.[4]

Study population

All HIV-negative (defined as no prior HIV diagnosis-related SHHAPT code) attendees aged 16 years or over attending SHCs in England during 2011-2014 were included in the study. Individuals prescribed PEPSE were those who had a clinical record with the appropriate SHHAPT code. 126 episodes (accounting for 78 attendees) of PEPSE were recorded after a HIV diagnosis-related SHHAPT code. These were assumed to be clinical coding errors and were excluded from further analysis. MSM were defined as men who had reported sex with another man (i.e. their sexual orientation was self-reported as homosexual or bisexual) at least once during their clinic attendance history.

Data analysis

Trends in the number of episodes where PEPSE was prescribed were assessed using quarterly data between 2011 and 2014. The Kolmogorov-Smirnov test was used to compare the overall increase by year in the number of episodes where PEPSE was prescribed by gender/sexual risk. We used the

British National Formulary (BNF) price for a 28-day course of PEPSE (£772 in March 2016) to estimate the annual drug cost based on the number of episodes where PEPSE was prescribed.

Risk factors for being prescribed PEPSE were identified in the population of HIV-negative MSM attendees who were allocated to two groups based on their attendance history during 2011-2014: (i) those prescribed PEPSE and (ii) those not prescribed PEPSE. Demographic characteristics (age, ethnicity, country of birth and clinic location) were explored using the first recorded episode where PEPSE was prescribed or the first attendance for those not prescribed PEPSE. Ethnicity was defined by patient self-report and categorised based on the national Census codes. Country of birth was reported as International Organisation for Standardisation codes and categorised according to Office for National Statistics (UK) regions. We investigated the proportion of MSM diagnosed with an acute bacterial STI (chlamydia, gonorrhoea or infectious syphilis) in the year prior to and at their first recorded PEPSE episode or first attendance. Univariate and multivariable logistic regression were used to investigate demographic and clinical risk factors associated with PEPSE. Records with missing data on any of the variables were excluded (23,559 attendees out of a total of 253,496).

We used the Kaplan-Meier method to estimate the proportion of HIV-negative MSM attendees with a subsequent diagnosis code. To exclude incident HIV infections undiagnosed at the time of the PEPSE prescription, and to discount PEPSE failure, time at risk for HIV began four months after starting the most recent PEPSE course. This was based on the UK guidelines for PEPSE at the time (2011) which recommended follow-up HIV testing twelve weeks post-completion of the PEPSE course.[5] Those not prescribed PEPSE were considered to be at risk from four months after their first attendance. MSM were censored at their HIV diagnosis or at the end of the follow-up period (30th September 2015). MSM whose first attendance was less than 4 months before the end of the follow-up period were excluded. Where no HIV code was reported, we assumed that MSM remained HIV negative regardless of whether they returned for a subsequent HIV test. Log rank tests were used to compare survival curves by the number of PEPSE courses prescribed and by the following risk profiles:

(i) No PEPSE courses and no bacterial STI in the past 12 months

(ii) At least one PEPSE course and no bacterial STI in the past 12 months

(iii) No PEPSE courses and a bacterial STI in the past 12 months

(iv) At least one PEPSE course and a bacterial STI in the past 12 months

Cox proportional hazards models were used to estimate hazard ratios and to adjust for confounders (age, ethnicity, region of birth and clinic location). Records with missing data on any of the variables were excluded from the modelling (23,493 attendees out of a total of 252,257).

A sensitivity analysis was conducted to explore a more conservative censoring method; MSM were censored at their HIV diagnosis or the last HIV test. MSM with no subsequent HIV test were excluded from this sensitivity model resulting in a reduced study population of 88,431 (excluding 6,332 with missing data).

RESULTS

During 2011-2014, there were 24,004 episodes where PEPSE was prescribed at SHCs in England: 16,422 (68%) were prescribed to MSM, 3,333 (14%) were prescribed to heterosexual men and 3,963 (17%) were prescribed to women.

The number of episodes where PEPSE was prescribed to MSM increased from 370 in the first calendar quarter (Q1) of 2011 to 1,632 in Q4 of 2014, with the steepest increase between Q2 and Q3 of 2011 (70%). The overall increase in the number of episodes where PEPSE was prescribed by year was significantly greater for MSM (150%; 2,382 to 5,944) compared to heterosexual men (62%; 625 to 1,104) and women (60%; 759 to 1,212), ($p<0.001$, Kolmogorov-Smirnov test) (figure 1). The estimated drug cost of PEPSE prescribing in 2014 was over £6 million per year, with £4.5 million attributable to MSM. There was a year-on-year increase in the proportion of all MSM attendees at SHCs who were prescribed PEPSE (2.01% in 2011 to 3.82% in 2014) (online supplementary table).

During 2011-2014, 13,453 MSM attendees were prescribed PEPSE. 15% (1,981) were prescribed more than one course; of these, 71% (1,412) were prescribed 2 courses of PEPSE and 29% (569) 3 or more courses (maximum 13 courses). Among MSM prescribed more than one course, 60% (1,194/1,981) received a second course less than 6 months after the first course. The proportion of MSM attendees prescribed multiple courses (2 or more) within a given calendar year did not change; 12.4% (254/2,055) in 2011 compared to 9.9% (520/5,282) in 2014.

Of MSM attendees prescribed PEPSE, 45% (6,051/13,447) were aged 25-34 years, 80% (10,171/12,784) were white and 63% (7,975/12,679) were born in the UK. Two thirds (67%; 9,033) were prescribed PEPSE at a London-based service. 54% (7,229) had a prior attendance recorded at the same SHC since 2008, of which 83% (5,960) had attended at least once in the previous year. This was higher than the prior attendance rate for MSM not prescribed PEPSE; 18% (44,004/240,043) had a prior attendance, of which 42% (18,506) had attended at least once in the previous year. 5.4% (725)

of MSM prescribed PEPSE were diagnosed with at least one acute bacterial STI at the same attendance as the PEPSE prescription; 3.3% (443) were diagnosed with gonorrhoea, 2.1% (287) with chlamydia and <1% (57) with infectious syphilis. 10.8% (1,446) of all MSM prescribed PEPSE had been diagnosed with at least one acute bacterial STI in the previous year; 7.2% (974) were diagnosed with gonorrhoea, 4.8% (648) with chlamydia and <1% (112) with infectious syphilis. Among all MSM not prescribed PEPSE, 11.8% (28,455) had at least one acute bacterial STI at their first attendance; 6.9% (16,642) were diagnosed with gonorrhoea, 5.1% (12,238) with chlamydia and 1% (2,415) with infectious syphilis. Only 1.1% (2,574) of all MSM not prescribed PEPSE had been previously diagnosed with at least one acute bacterial STI.

In the multivariable analysis, MSM prescribed PEPSE were more likely to be aged 25-44 years, be born outside of the UK, particularly sub-Saharan Africa [aOR(95% CI): 1.27(1.13-1.43)] or the Caribbean [aOR(95% CI): 1.36(1.08-1.72) (table 1), be of mixed, [aOR(95% CI):1.29(1.17-1.41)] or black other (non-Caribbean/non-African) ethnicity [aOR(95% CI)1.23(1.01-1.51)] compared to White ethnicity, and to have attended a SHC in London [aOR(95% CI):0.56(0.53-0.58) for non-London versus London SHCs]. MSM prescribed PEPSE were less likely to be diagnosed with an acute bacterial STI at the same attendance [aOR(95% CI) – gonorrhoea: 0.45(0.40-0.50); chlamydia: 0.44(0.39-0.50); syphilis: 0.51(0.39-0.67)] but were more likely to have had a bacterial STI in the 12 months prior to the PEPSE prescription [aOR(95% CI) – gonorrhoea: 11.6(10.5-12.8); chlamydia: 5.02(4.46-5.67); syphilis: 2.25(1.73-2.93)]. The positive association between a previous bacterial STI diagnosis and PEPSE remained after adjusting for the number of prior attendances (data not shown).

193 *Table 1: Independent risk factors associated with the first reported episode where PEPSE was*
194 *prescribed in MSM attendees, England, 2011-2014*

Variable	Number of attendees n=229,937	PEPSE use n=12,289 (5.3%, (n/N%))	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted p value
Age group (years)					
<20	13,277	507 (3.8%)	0.57 (0.52-0.62)	0.76 (0.69-0.84)	<0.001
20-24	46,204	2,164 (4.7%)	0.70 (0.67-0.74)	0.81 (0.77-0.86)	<0.001
25-34	84,162	5,491 (6.5%)	1	1	
35-44	46,494	2,869 (6.2%)	0.94 (0.90-0.99)	0.96 (0.91-1.00)	0.066
≥45	39,800	1,258 (3.2%)	0.47 (0.44-0.50)	0.53 (0.50-0.56)	<0.001
Ethnic group					
White	194,691	9,812 (5.0%)	1	1	
Asian	10,707	695 (6.5%)	1.31 (1.21-1.42)	1.03 (0.95-1.13)	0.456
Black Caribbean	3,427	217 (6.3%)	1.27 (1.11-1.46)	1.01 (0.86-1.18)	0.944
Black African	3,166	221 (7.0%)	1.41 (1.23-1.62)	0.99 (0.85-1.17)	0.939
Black other	1,467	117 (8.0%)	1.63 (1.35-1.97)	1.23 (1.01-1.51)	0.039
Mixed	7,621	585 (7.7%)	1.57 (1.44-1.71)	1.29 (1.17-1.41)	<0.001
Other	8,858	642 (7.3%)	1.47 (1.36-1.60)	1.08 (0.99-1.19)	0.089
Region of Birth					
UK	166,832	7,722 (4.6%)	1	1	
Europe (non-UK)	30,039	2,084 (6.9%)	1.54 (1.46-1.62)	1.12 (1.06-1.18)	<0.001
Caribbean	1,244	102 (8.2%)	1.84 (1.50-2.26)	1.36 (1.08-1.72)	0.009
Sub-Saharan Africa	5,756	439 (7.6%)	1.70 (1.54-1.88)	1.27 (1.13-1.43)	<0.001
Other	26,066	1,942 (7.5%)	1.66 (1.57-1.75)	1.18 (1.10-1.25)	<0.001
SHC location					
London	115,959	8,185 (7.1%)	1	1	
Outside London	113,978	4,104 (3.6%)	0.49 (0.47-0.51)	0.56 (0.53-0.58)	<0.001

Coincident gonorrhoea					
No	214,366	11,889 (5.6%)	1	1	
Yes	15,571	400 (2.6%)	0.45 (0.41-0.50)	0.45 (0.40-0.50)	<0.001
Coincident chlamydia					
No	218,498	12,027 (5.5%)	1	1	
Yes	11,439	262 (2.3%)	0.40 (0.36-0.46)	0.44 (0.39-0.50)	<0.001
Coincident syphilis					
No	227,685	12,233 (5.4%)	1	1	
Yes	2,252	56 (2.5%)	0.45 (0.34-0.59)	0.51 (0.39-0.67)	<0.001
History of gonorrhoea					
No	227,971	11,369 (5.0%)	1	1	
Yes	1,966	920 (46.8%)	16.8 (15.3-18.4)	11.6 (10.5-12.8)	<0.001
History of chlamydia					
No	228,106	11,695 (5.1%)	1	1	
Yes	1,831	594 (32.4%)	8.89 (8.04-9.82)	5.02 (4.46-5.67)	<0.001
History of syphilis					
No	229,444	12,188 (5.3%)	1	1	
Yes	493	101 (20.5%)	4.59 (3.69-5.72)	2.25 (1.73-2.93)	<0.001

OR, Odds Ratio; CI, confidence interval. Unadjusted and adjusted odds ratios calculated using logistic regression. Adjusted for all variables listed in the table only. Infectious syphilis includes primary, secondary and early latent diagnoses. Mixed ethnicity includes white and black Caribbean, white and black African, white and Asian or other mixed background.

Overall, 255 (1.9%) MSM attendees prescribed PEPSE and 1,817 (0.8%) MSM not prescribed PEPSE were subsequently diagnosed with HIV with estimated HIV diagnosis rates of 9.7 per 1000 person-years (95%CI 8.6-11.0) and 3.0 per 1000 person years (95% CI 2.8-3.1), respectively. The HIV diagnosis rate was considerably higher among MSM attendees who were prescribed two or more courses of PEPSE (18.2 per 1000 person-years (95% CI 14.1-23.6) compared to those prescribed one course (8.5 per 1000 person-years (95% CI 7.4-9.8) (figure 2a and table 2a). In the sensitivity analysis, MSM prescribed PEPSE had a HIV diagnosis rate of 38.5 per 1000 person-years (95% CI 34.0-43.5) compared to 13.6 per 1000 person-years (95% CI 12.9-14.2) among those not prescribed PEPSE. The HIV diagnosis rate for MSM prescribed 2 or more courses of PEPSE was 50.8 per 1000 person-years (95% CI 39.1-66.0) compared to 35.9 per 1000 person-years (95% CI 31.2-41.4) for MSM prescribed one course. This association was only weakly significant reflective of the smaller study population.

The probability of a HIV diagnosis varied according to risk profiles; MSM prescribed PEPSE and with a bacterial STI in the past 12 months had a considerably higher rate of HIV diagnosis (24.1 per 1000 person-years (95%CI 19.1-30.5) when compared to all other risk profiling groups (figure 2b). The HIV diagnosis rate was 6-fold higher compared to those with the lowest risk profile (table 2b). In the sensitivity analysis, the same general trends were observed (data not shown).

Table 2: Unadjusted and adjusted Hazard ratios for subsequent HIV infection risk in MSM, 2011-2014

a) by the number of PEPSE courses

**Total person-years at risk to the nearest whole number*

	Persons at risk n=228,764	Total person-years at risk*	Number of new HIV diagnoses n=1,980	Unadjusted HR (95% CI)	Adjusted HR (95% CI)**	Adjusted p value**
Number of PEPSE courses						
None	216,581	552,957	1,733	1	1	
Single	10,352	20,558	189	2.72 (2.34-3.16)	2.54 (2.19-2.96)	<0.001
Multiple	1,831	2,968	58	5.50 (4.23-7.14)	4.80 (3.69-6.25)	<0.001

***Analysis adjusted for age, ethnic group, world region of birth and SHC location. HR, Hazard ratio; CI, confidence interval. Adjusted and unadjusted hazard ratios calculated using Cox Proportional Hazards model*

b) by clinical risk profiles

	Persons at risk n=228,764	Total person-years at risk*	Number of new HIV diagnoses n=1,980	Unadjusted HR (95% CI)	Adjusted HR (95% CI)**	Adjusted p value*
Risk Strata						
No PEPSE, No STI	214,192	543135	1,637	1	1	
PEPSE, No STI	10,569	20847	178	2.62 (2.25-3.06)	2.44 (2.09-2.86)	<0.001
No PEPSE, STI	2,389	9822	96	3.83 (3.11-4.70)	3.98 (3.24-4.90)	<0.001

PEPSE, STI	1,614	2679	69	7.58 (5.95-9.64)	6.61 (5.19-8.42)	<0.001

225 **Total person-years at risk to the nearest whole number*

226 **Analysis adjusted for age, ethnic group, world region of birth and SHC location. HR, Hazard ratio; CI,*
227 *confidence interval. Adjusted and unadjusted hazard ratios calculated using Cox Proportional Hazards*
228 *model*

229

DISCUSSION

Main findings

The number of episodes where PEPSE was prescribed to MSM increased substantially and more rapidly than for heterosexual men and women. 13,453 (4.5% overall) MSM attendees at SHCs in England during 2011-2014 were prescribed at least one episode of PEPSE and repeat prescribing was common (15% were prescribed two or more courses). MSM attendees diagnosed with a bacterial STI in the past 12 months were between 2 and 12-times more likely to be prescribed PEPSE compared to those without a previous STI infection. Of note, MSM prescribed PEPSE, and in particular those prescribed two or more courses of PEPSE, were at high risk of subsequent HIV acquisition.

Strengths and Limitations

The strength of this study lies in the interrogation of national surveillance data with mandatory reporting from all specialist SHCs in England. The scale and detail of data using standardised reporting definitions are unprecedented and this study therefore provides a unique overview of PEPSE prescribing to inform clinical decision making and resource allocation.

This study has several limitations. First, although GUMCADv2 provides patient-level data it is not possible to track patients between clinics. In a pilot study, 15% of MSM reported ever attending another SHC, [6] and this may be more common in urban settings like London[7], which might lead to underestimation of HIV acquisition and repeat PEPSE prescribing in our study. Second, we have assumed that MSM were HIV negative until the end of follow-up time in the Kaplan-Meier analysis, unless they had a new HIV diagnosis, which might also underestimate HIV acquisition. However, the results of the sensitivity analysis, in which a more conservative approach was taken, were in accordance with the original model. Third, reporting of PEPSE prescribing was introduced in 2011 and there was an initial and expected lag phase in reporting such that overall PEPSE prescribing may be underestimated in our analysis during the early stages of 2011. However, we are confident that PEPSE

coding was fully integrated into clinical practice by mid-2011, as implied by the fact that the trend lines for heterosexual males and females remain relatively stable after this time (figure 1) and thus the impact is likely to be minimal. Fourth, sexual behaviour is strongly associated with both PEPSE use and HIV acquisition and the absence of these data limited our ability to interpret associations in our analyses. We used data on previous STI acquisition as a proxy measure for high-risk behaviour as this is a known predictor of HIV infection.[8]

Interpretation

We found a strong association between PEPSE use and a previous bacterial STI infection which suggests that MSM prescribed PEPSE represent a group with higher risk behaviours, as has been reported elsewhere. [9,10] The fact that MSM prescribed PEPSE were less likely to present with a bacterial STI at their attendance for PEPSE was expected, since PEPSE is provided within 72 hours of a sexual risk exposure when any STI is not likely to be detectable. MSM prescribed PEPSE were at high-risk of HIV acquisition and the strong association between the number of PEPSE courses prescribed and the rate of HIV diagnosis suggests that PEPSE is a marker of on-going risk behaviour. Several observational studies have reported HIV seroconversion after receiving PEPSE due to ongoing risk behaviour and re-exposure to HIV.[11-13] PEPSE use among a community cohort of MSM in Australia did not lead to a reduction in risk behaviour and those prescribed PEPSE had a higher rate of subsequent HIV seroconversion.[11] A retrospective review of MSM attending an urban health centre in Boston for PEPSE found no association between repeat PEPSE use and HIV infection risk compared with single PEPSE use, which differs from our results. However, the number of participants was smaller. [13] The association between a previous bacterial STI infection and HIV acquisition has been found elsewhere [14-16] and our study identified a particular sub-set of MSM prescribed PEPSE and with a previous bacterial STI that had the highest rate of HIV diagnosis.

Implications

In recent years, PEPSE use as an HIV prevention measure among MSM has increased and there is no indication that this will change. The overall cost is high (£4.5 million in MSM) despite the weak evidence base for its clinical effectiveness.[5] We have shown that PEPSE is a strong marker of subsequent risk behaviour and HIV acquisition among MSM attending SHCs and thus accessing a high standard of preventative care. In our analysis, 15% of MSM were prescribed PEPSE more than once at the same clinic and exhibited a 5-fold increased risk of acquiring HIV infection despite receiving counselling and advice on risk reduction strategies. MSM prescribed PEPSE, and especially those returning for repeat PEPSE would benefit from more intensive risk reduction interventions.[1] Furthermore, national trends show a steadily increasing number of HIV diagnoses in MSM, and evidence from community-based surveys of sexual behaviour in MSM suggest that there is a need to enhance the existing HIV prevention package. Community based surveys have shown increases in UAI with casual partners,[16,17] self-reported STIs,[16] and UAI with a main partner of a different HIV status.[18]

A number of well-designed RCTs have demonstrated the very strong effectiveness of pre-exposure prophylaxis (PrEP) for preventing HIV infection among gay, bisexual and other MSM,[19,20] and support the inclusion of PrEP within a multicomponent HIV prevention package for MSM at risk, incorporating behavioural, structural and biomedical approaches based on robust scientific evidence.[21] In the deferred arm of the PROUD study (i.e. those who received PrEP after a deferral period of 1 year), PEPSE prescribing was common but HIV incidence was also very high.[19] Any HIV-PrEP programme is likely to be delivered through SHCs and reduce the number of MSM prescribed PEPSE and their subsequent risk of HIV acquisition. Furthermore, survey data suggest that MSM prescribed PEPSE are more likely to consider PrEP compared to those with no experience of PEPSE.[22] Of course, the value of PrEP is closely related to HIV incidence in various sub-groups of the high-risk population and the cost savings that can be achieved, which is beyond the scope of this study.

Overall, we found that the number of episodes where PEPSE was prescribed has increased markedly in MSM, and that MSM attendees prescribed PEPSE are at sustained increased risk of acquiring HIV. This information is directly actionable, by supporting MSM who have been prescribed PEPSE to reduce sexual behavioural risk, and these MSM may be an appropriate group to target with PrEP. Biomedical interventions, like PrEP, in combination with other HIV prevention strategies including condom promotion, behavioural change and increased HIV testing may be beneficial for MSM that present for PEPSE, particularly those who have been previously diagnosed with a bacterial STI.

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AUTHOR CONTRIBUTIONS

HM conducted the analyses and drafted the first version of the manuscript; MF contributed towards the analyses; all authors contributed towards the study design, interpretation of the data, iterations of the paper, and approved the final version of the paper submitted for publication.

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ETHICS STATEMENT

As GUMCADv2 is a routine public health surveillance activity, no specific consent was required from the patients whose data were used in this analysis. PHE has permission to handle data obtained by GUMCADv2 under section 251 of the UK National Health Service Act of 2006 (previously section 60 of the Health and Social Care Act of 2001), which was renewed annually by the ethics and confidentiality committee of the National Information Governance Board until 2013. Since then the power of approval of public health surveillance activity has been granted directly to PHE.

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404 **FIGURE LEGENDS**

405

406 *Figure 1: Trends in the number of episodes where PEPSE was prescribed by gender & sexual risk,*

407 *England, 2011-2014*

408

409 *Figure 2: Kaplan-Meier curves showing time to HIV diagnosis among MSM attendees, 2011-2014:*

410 *a) by the number of PEPSE courses prescribed*

411 *b) by clinical risk profiles*

412