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Intensified shigellosis epidemic associated with sexual transmission in men who have sex with men - *Shigella flexneri* and *S. sonnei* in England, 2004 to end of February 2015

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Surveillance data suggest an intensification of the shigellosis epidemic associated with sexual transmission in men who have sex with men (MSM) in England with separate introductions into the population. In 2014, sexual transmission between MSM might have accounted for 97%, 89%, and 43% of non-travel associated *Shigella flexneri* 3a and *S. flexneri* 2a, and *S. sonnei* diagnoses. Clinicians should sensitively ascertain sexual history for men with enteric infections to facilitate prompt diagnosis and appropriate management.

Intensification of shigellosis transmission between men who have sex with men

Laboratory diagnoses of *Shigella flexneri* 2a in adult men without a reported travel history have increased markedly from 73 cases in 2013 to 220 cases in 2014 in England, while diagnoses in women have remained low (13 cases for each year). *S. sonnei* diagnoses in men have increased from 189 cases to 267 cases over the same period, again without increases in women. This pattern mirrors an earlier epidemic, from 2009, of *S. flexneri* 3a associated with sexual transmission between men. Here we report preliminary data suggesting an intensification of the shigellosis epidemic associated with sex between men in England continuing into 2015.

Background

There are four species of Gram-negative bacteria of the genus *Shigella* that cause severe bacillary dysentery in humans (*S. flexneri*, *S. sonnei*, *S. boydii*, and *S. dysenteriae*) with over 50 serotypes described. Although many cases in England are associated with travel to high-incidence regions such as the Indian subcontinent, North and East Africa and South America, outbreaks of *S. flexneri* and *S. sonnei* associated with sexual transmission between men who have sex with men (MSM) have been reported in the United Kingdom (UK), Germany, Spain, Australia, Canada and the United States [1-9].

Shigella reporting in England

Faecal specimens from cases with symptoms of gastrointestinal infection are submitted to local hospital, private and regional laboratories in England for culture of Shiga toxin-producing *Escherichia coli*, *Salmonella*, *Campylobacter* and *Shigella* species. Local hospital laboratories are recommended to submit presumptive strains of *Shigella flexneri* and other *Shigella* spp. to the Public Health England (PHE) national reference laboratory in London, the Gastrointestinal Bacteria Reference Unit (GBRU), for confirmation and typing, using standard biochemistry and serological tests [10]. Neither sexual behaviour nor orientation are routinely collected in this dataset, but the number of cases associated with sexual transmission among men may be approximated by using the GBRU typing data to identify diagnoses for men and women aged 16 to 60 years and excluding cases where recent travel outside the UK was reported. Given an assumption that equal numbers of men and women would be affected if transmission between men were not a risk factor, excess male cases are deemed likely to be in MSM.

We have previously reported a national outbreak and investigation of *S. flexneri* 3a occurring in MSM between 2009 and 2011 [11]. Most of these were white, UK-born MSM, many were HIV-positive, and they reported being part of dense sexual networks involving high numbers of casual and regular partners. This outbreak was associated with (i) low awareness about the risk of enteric infections, (ii) chemsex (sexual activity while under the influence of [typically] stimulant drugs), and (iii) meeting sex partners and locating sex parties through social and sexual networking applications [12,13].

Table

Patients aged 16 to 60 years diagnosed with *Shigella* spp. infection with no reported history of travel outside the United Kingdom, by sex, and male to female sex ratios, England, 2004–2014 (n=4,909)

Shigella species	Serotype	Sex and sex ratio	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Total
S. flexneri	1b	Male	8	6	16	18	12	9	8	9	17	7	9	119
		Female	5	2	6	5	7	8	4	5	7	10	4	63
		Ratio	1.6	**3.0**	**2.7**	**3.6**	1.7	1.1	**2.0**	1.8	**2.4**	0.7	**2.3**	1.9
	2a	Male	9	21	27	18	22	23	50	30	42	73	220	535
		Female	8	16	28	21	18	17	14	21	12	13	13	181
		Ratio	1.1	1.3	1.0	0.9	1.2	1.4	**3.6**	1.4	**3.5**	**5.6**	**16.9**	**3.0**
	3a	Male	3	6	11	11	18	65	77	83	85	154	118	631
		Female	5	5	5	6	8	8	9	10	10	15	2	83
		Ratio	0.6	1.2	**2.2**	1.8	**2.3**	**8.1**	**8.6**	**8.3**	**8.5**	**10.3**	**59.0**	**7.6**
	6	Male	4	5	10	12	4	6	6	9	11	8	4	79
		Female	1	10	14	9	13	14	15	12	11	7	2	108
		Ratio	**4.0**	0.5	0.7	1.3	0.3	0.4	0.4	0.8	1.0	1.1	**2.0**	0.7
	Other	Male	11	6	9	21	15	14	33	31	45	37	36	258
		Female	7	4	13	9	6	15	15	13	11	14	12	119
		Ratio	1.6	1.5	0.7	**2.3**	**2.5**	0.9	**2.2**	**2.4**	**4.1**	**2.6**	**3.0**	**2.2**
S. sonnei	NA	Male	76	73	52	85	83	87	147	135	144	189	267	1,338
		Female	48	71	89	119	94	125	133	84	63	95	106	1,027
		Ratio	1.6	1.0	0.6	0.7	0.9	0.7	1.1	1.6	**2.3**	**2.0**	**2.5**	1.3
S. boydii	NA	Male	9	7	17	14	12	5	10	5	5	13	9	106
		Female	4	11	13	16	17	9	20	11	9	12	9	131
		Ratio	**2.3**	0.6	1.3	0.9	0.7	0.6	0.5	0.5	0.6	1.1	1.0	0.8
S. dysenteriae	NA	Male	2	2	2	3	12	2	7	2	4	1	2	39
		Female	2	6	4	10	4	4	9	7	9	2	5	62
		Ratio	1.0	0.3	0.5	0.3	**3.0**	0.5	0.8	0.3	0.4	0.5	0.4	0.6
Species unidentified	NA	Male	1	3	3	5	2	0	0	0	0	1	0	15
		Female	2	3	5	3	1	0	1	0	0	0	0	15
		Ratio	0.5	1.0	0.6	1.7	**2.0**	NA	0.0	NA	NA	NA	NA	1.0
Total	NA	NA	205	257	324	385	348	411	558	467	485	651	818	4,909

NA: not applicable.
The male to female sex ratios ≥ 2.0 are highlighted in bold.

Recent trends in shigellosis in England

We examined recent trends in national *Shigella* spp. diagnoses to explore whether there is evidence for (i) ongoing sexual transmission of *S. flexneri* 3a and (ii) transmission of other *Shigella* serotypes or species among men.

Between 1 January 2004 and 28 February 2015, the total number of *Shigella* spp. diagnoses in England among 16 to 60 year olds was 9,534 and of these, 5,051 (53%) were not known to be associated with travel outside the UK. Among those without recent travel history, diagnoses of *S. flexneri* 3a, *S. flexneri* 2a, and *S. sonnei* accounted for 77% (3,795/4,909) of all cases (Table). During the study period, 262 unique laboratories submitted isolates of *S. flexneri* and 254 laboratories submitted isolates of *S. sonnei*.

Diagnoses of *S. flexneri* 3a in men increased steadily from 2004 to 2013 (from 3 to 154 cases) and fell in 2014 (118 cases), with sharp increases noted in 2009 and 2013; diagnoses in women during this period remained low (Table; Figure 1A). Diagnoses of *S. flexneri* 2a in men followed a similar pattern, although increases emerged later, rising from a baseline of nine cases in 2004 with peaks in 2010 (50 cases) and 2014 (220 cases); diagnoses in women during this period remained low (Table; Figure 1A). Diagnoses of *S. sonnei* in men began to exceed those in women (147 compared with 133 cases) in 2010, and have since risen steadily in men (267 cases in 2014) while remaining stable in women (Table; Figure 1B).

Male to female sex ratios also rose substantially during this period, and peaked in 2014 at 59.0:1, 16.9:1 and 2.5:1 for *S. flexneri* 3a, *S. flexneri* 2a, and *S. sonnei* (Table). The age distribution for cases of *S. flexneri* 3a, *S. flexneri* 2a, and *S. sonnei* was similar for men and women: 65% (1,629/2,504) of male cases and 61% (783/1,291) of female cases were in those aged 25 to 44 years. However, geographic distribution differed: 64% (1,574/2,504) of male cases of *S. flexneri* 2a, *S. flexneri* 3a and *S. sonnei* were reported by laboratories in London, Manchester, or Brighton, whereas only 38% (491/1,291) of female cases were from these areas.

In 2014, among those with no recent travel history and assuming all excess male cases were in MSM, we approximate that 116 cases of *S. flexneri* 3a (97% of all excess cases), 207 of *S. flexneri* 2a (89%), and 161 of *S. sonnei* (43%) might have been acquired through sex between MSM.

High levels of transmission of *S. flexneri* 3a, *S. flexneri* 2a, and *S. sonnei* in men have been sustained into 2015 (Figure 2). Monthly reporting data suggest that a switch in the predominant serotype of *S. flexneri* from type 3a to type 2a occurred from March 2014.

Discussion and conclusion

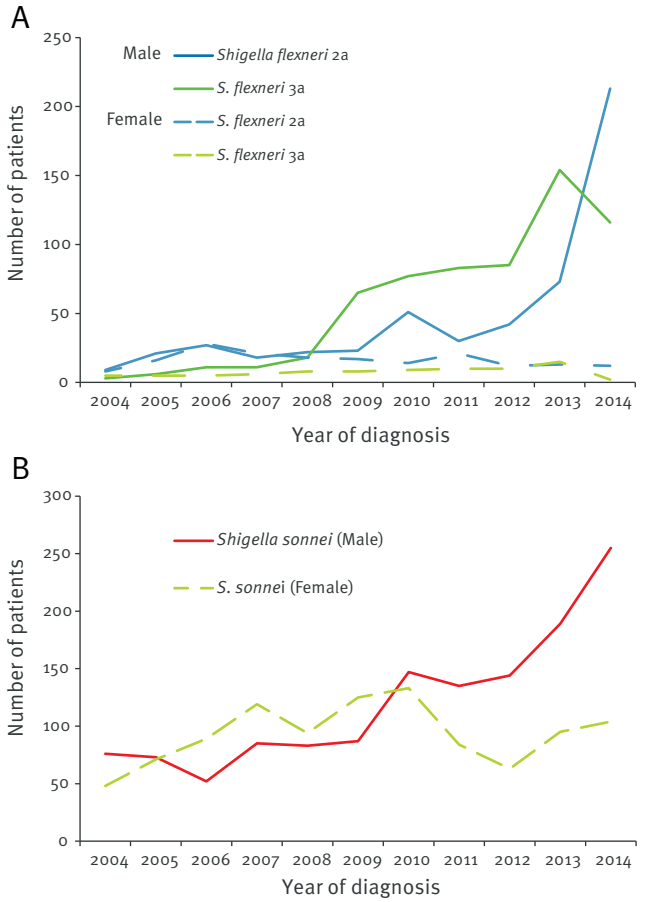
Laboratory data over an 11-year period show ongoing endemic transmission of *S. flexneri* 3a among men since 2009, and emerging epidemics of *S. flexneri* 2a and *S. sonnei* among men since 2011. Diagnoses in women during the same period have remained stable or declined. These data strongly suggest an intensification of the previously reported shigellosis epidemic in England associated with sexual transmission between MSM. The actual numbers are probably underestimated due to individuals in the community not seeking healthcare or not providing diagnostic stool specimens.

Early investigations into the *S. flexneri* 3a outbreak in 2011 failed to identify a point source and found most cases occurred in MSM [11-13]. The present analysis lacks sexual behaviour data, but the concentration of shigellosis diagnoses in urban settings, where we know rates of HIV, gonorrhoea and syphilis in MSM are high, and the increase in specific strains and serotypes found in adult men and not women is consistent with most likely continued sexual transmission of *Shigella* spp. among MSM. Nevertheless, there are other possible explanations for the excess in men. While reporting guidelines have not changed during the study period, some reporting practices may have changed leading to more samples obtained from men than from women being referred by laboratories. However, it seems unlikely that this would fully explain the extent of increases seen. Proactive campaigns have been undertaken by Public Health England (PHE) and the Terrence Higgins Trust (www.tht.org.uk/shigella) to alert general practitioners (GPs) and other health professionals to sexually transmissible enteric infections (STEI) in MSM and to raise awareness among MSM through social media, the gay press, and leaflets in health clinics. These campaigns may have increased healthcare seeking and diagnostic testing among men. However, the campaigns did not start until 2013, after increases in *Shigella* spp. diagnoses were first observed.

The emergence of these STEIs has coincided with increased diagnoses of gonorrhoea, lymphogranuloma venereum, infectious syphilis and a recent cluster of verocytotoxin-producing *Escherichia coli* 0117:H7 among MSM, particularly those co-infected with HIV [14-17]. The characteristics of men affected by these overlapping epidemics are very similar and

Figure 1

Patients aged 16 to 60 years diagnosed with (A) *Shigella flexneri* serotypes 2a and 3a (n=1,430) and (B) *S. sonnei* (n=2,365), with no reported history of travel outside the United Kingdom, by sex, England, 2004–2014

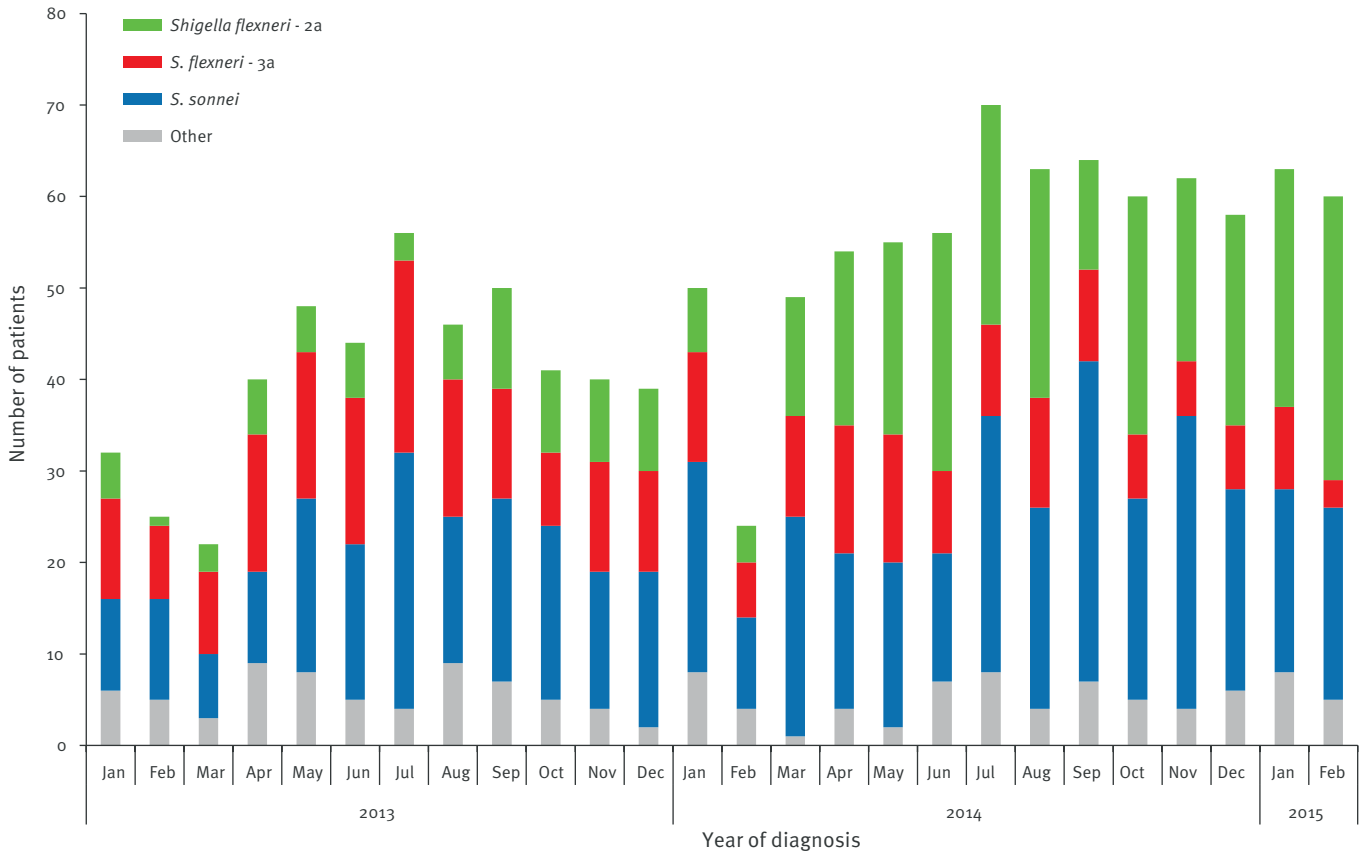


this suggests an intensification of sexual networking among HIV-diagnosed MSM engaging in HIV seroadaptive behaviours, possibly facilitated by geo-spatial apps [14-18]. Indeed, the different timing and heterogeneity in species and types indicate separate introductions of *Shigella* spp. into this population, and is consistent with this hypothesis.

Rapid intercontinental dissemination through sexual transmission in MSM of a *S. flexneri* 3a lineage with an azithromycin-resistance conferring plasmid has recently been demonstrated [19], and outbreaks of other STIs in MSM can spread quickly across Europe [20]. There is evidence that MSM may be more likely to engage in sexual risk behaviours while travelling abroad [21], raising the possibility of shigellosis outbreaks occurring elsewhere in Europe. We are currently reviewing laboratory reports of other enteric pathogens to explore whether sex between men might be an important route of transmission. MSM with symptoms of enteric pathogens may present to a range of healthcare settings including primary care, emergency departments, and specialist sexual health and gastroenterology services. To limit missed diagnostic opportunities, facilitate prompt diagnosis and appropriate

Figure 2

Men aged 16 to 60 years diagnosed with *Shigella flexneri* 2a, *S. flexneri* 3a, and *S. sonnei* with no reported history of travel outside the United Kingdom, by month, England, January 2013–February 2015 (n=1,271)



management, including partner notification and appropriate antibiotic stewardship, healthcare professionals need to recognise the potential for STEIs in MSM and sensitively ascertain sexual history. Public health actions for shigellosis cases are described [22], but for MSM they should additionally include advice about when to resume sexual activity, partner notification, preventative advice about risky sexual behaviours, and screening for co-infection with STIs.

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Conflict of interest

None declared.

Authors' contributions

IS, NF, and GH drafted the manuscript. TC undertook data analysis assisted by CJ and TJD. VLG, PM and PDC contributed to data interpretation and revised the manuscript.

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Contribution of transmission in HIV-positive men who have sex with men to evolving epidemics of sexually transmitted infections in England: an analysis using multiple data sources, 2009–2013

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HIV seroadaptive behaviours may have contributed to greater sexually transmitted infection (STI) transmission in HIV-positive men who have sex with men (MSM) and to the global increase in STIs. Using multiple national surveillance data sources and population survey data, we estimated the risk of STIs in HIV-positive MSM and assessed whether transmission in HIV-positive MSM has contributed to recent STI epidemics in England. Since 2009, an increasing proportion of STIs has been diagnosed in HIV-positive MSM, and currently, the population rate of acute bacterial STIs is up to four times that of HIV-negative or undiagnosed MSM. Almost one in five of all diagnosed HIV-positive MSM in England had an acute STI diagnosed in 2013. From 2009 to 2013, the odds of being diagnosed with syphilis increased from 2.71 (95% confidence interval (CI) 2.41–3.05, p<0.001) to 4.05 (95% CI 3.70-4.45, p<0.001) in HIV-positive relative to HIV-negative/undiagnosed MSM. Similar trends were seen for gonorrhoea and chlamydia. Bacterial STI re-infection rates were considerably higher in HIV-positive MSM over a five-year follow-up period, indicative of rapid transmission in more dense sexual networks. These findings strongly suggest that the sexual health of HIV-positive MSM in England is worsening, which merits augmented public health interventions and continued monitoring.

Introduction

The United Kingdom (UK) has seen a steady increase in diagnoses of sexually transmitted infections (STIs) in the last decade, in particular, in men who have sex with men (MSM). From 2012 to 2013, gonorrhoea and syphilis diagnoses in MSM increased by 26% and 12% respectively [1]. The emergence of resistance and reduced sensitivity to frontline treatments of gonorrhoea is of global concern and may have contributed to high levels of gonorrhoea transmission in MSM [2-4]. Additionally, outbreaks of less common STIs such as Lymphogranuloma venereum (LGV) [5], together with shigellosis (which can be sexually transmissible) [6] in this population are of particular concern.

There is increasing evidence that HIV-positive MSM in the UK are disproportionately affected by STIs. Recent data demonstrated that of MSM diagnosed with syphilis, 35% were HIV positive [7]. HIV-positive MSM have also been found to account for more than 80% of LGV cases [5]. In part, these observations may reflect seroadaptive behaviours in HIV-positive MSM [8], in which different sexual practices such as unprotected (i.e. condomless) anal intercourse are adopted according to the reported HIV status of both partners in order to reduce the risk of transmitting or acquiring HIV. Seroadaptive behaviours vary considerably and include serosorting (limiting sexual partners to those with the same HIV status as themselves), strategic positioning (adopting a specific sexual position according to the HIV status of one's partner), withdrawal before ejaculation, and negotiating around viral load [9]. However, seroadaptive behaviours may come at a cost of increased transmission of STIs [10-12].

The UK has a growing population of HIV-positive MSM [13] and recent studies suggest that they may be increasingly adopting seroadaptive behaviours [8,14]. In this study we used multiple surveillance data sources and population survey data to estimate the risk of STIs in HIV-positive MSM and assessed whether transmission in HIV-positive MSM has contributed to recent STI epidemics in England.

Methods

Sources of data

Descriptive and comparative data analyses of the incidence of STIs were undertaken using data from GUMCADv2 (Genitourinary Medicine Clinic Activity Dataset) [15]. The Survey of Prevalent HIV Infections Diagnosed (SOPHID) [16], the third National Survey

of Sexual Attitudes and Lifestyles (Natsal-3) [17] and census data from the Office for National Statistics (ONS) [18] were employed to estimate denominator populations.

GUMCADv2 is a mandatory electronic pseudo-anonymised (i.e. contains the sex, age and hospital/clinic number of each patient but no patient identifiable information such as name, date of birth or postcode of residence is included) [19] patient-level dataset submitted to Public Health England (PHE) by all genitourinary medicine (GUM) clinics in England. The dataset contains information on all STI diagnoses and services provided for each patient as well as information on patient demographic such as sexual orientation, age, sex, ethnicity, area of residence and country of birth [19]. A unique patient identifier is assigned to each patient attending a given GUM clinic, allowing subsequent visits by the same patient to the same clinic to be identified.

SOPHID is a cross-sectional survey of all persons with diagnosed HIV infection who attend for HIV care at an NHS site in England, Wales and Northern Ireland. Age, sex, probable route of HIV infection, ethnicity, antiretroviral therapy (ART) status, CD4 cell count, region of residence and region of care provider are measured for each calendar year.

Natsal-3 is a nationally representative survey conducted between 2010 and 2012 on 15,162 individuals and provides information on key sexual behaviours, risk factors and also includes biological sampling and testing.

ONS is the national statistical institute for the UK and is responsible for collecting and publishing statistics related to the economy, population and society at national, regional and local levels.

Study population

MSM were defined as men who reported a homosexual or bisexual orientation at least once over the study period. MSM were defined as diagnosed HIV positive (hereafter referred to as 'HIV-positive' MSM) if they were diagnosed with HIV at least six weeks before their STI diagnosis, as newly diagnosed with HIV if they were diagnosed within six weeks of their STI diagnosis, and as HIV-negative/undiagnosed if there was no evidence of an HIV diagnosis in their GUMCADv2 record. For the analysis of acute STIs, STI population rates and association between STI outcomes and HIV status, MSM with new HIV diagnoses were grouped with those of negative or unknown status and referred to collectively as 'HIV-negative/undiagnosed', as the newly diagnosed men were assumed to be undiagnosed at the time of their STI exposure.

Data analysis

Acute sexually transmitted infections in known HIV-positive men who have sex with men

Episodes of acute STI diagnoses including gonorrhoea (acute and complicated), syphilis (primary, secondary and early latent), chlamydia, genital warts (first episode) and genital herpes (first episode) and HIV status in MSM were identified using Sexual Health and HIV Activity Property Type (SHHAPT) codes from GUMCADv2 for the years 2008 to 2013. Acute gonorrhoea includes all new cases of uncomplicated gonorrhoea of the lower genitourinary tract, anorectum, mouth, throat and adult conjunctivitis; complicated gonorrhoea includes all upper genitourinary tract complications (such as pelvic inflammatory disease and epididymitis) and systemic complications [20]. The proportion of STI diagnoses which were in HIV-positive MSM was calculated for each STI by year.

Sexually transmitted infection population rates in HIV-negative/undiagnosed and HIV-positive men who have sex with men

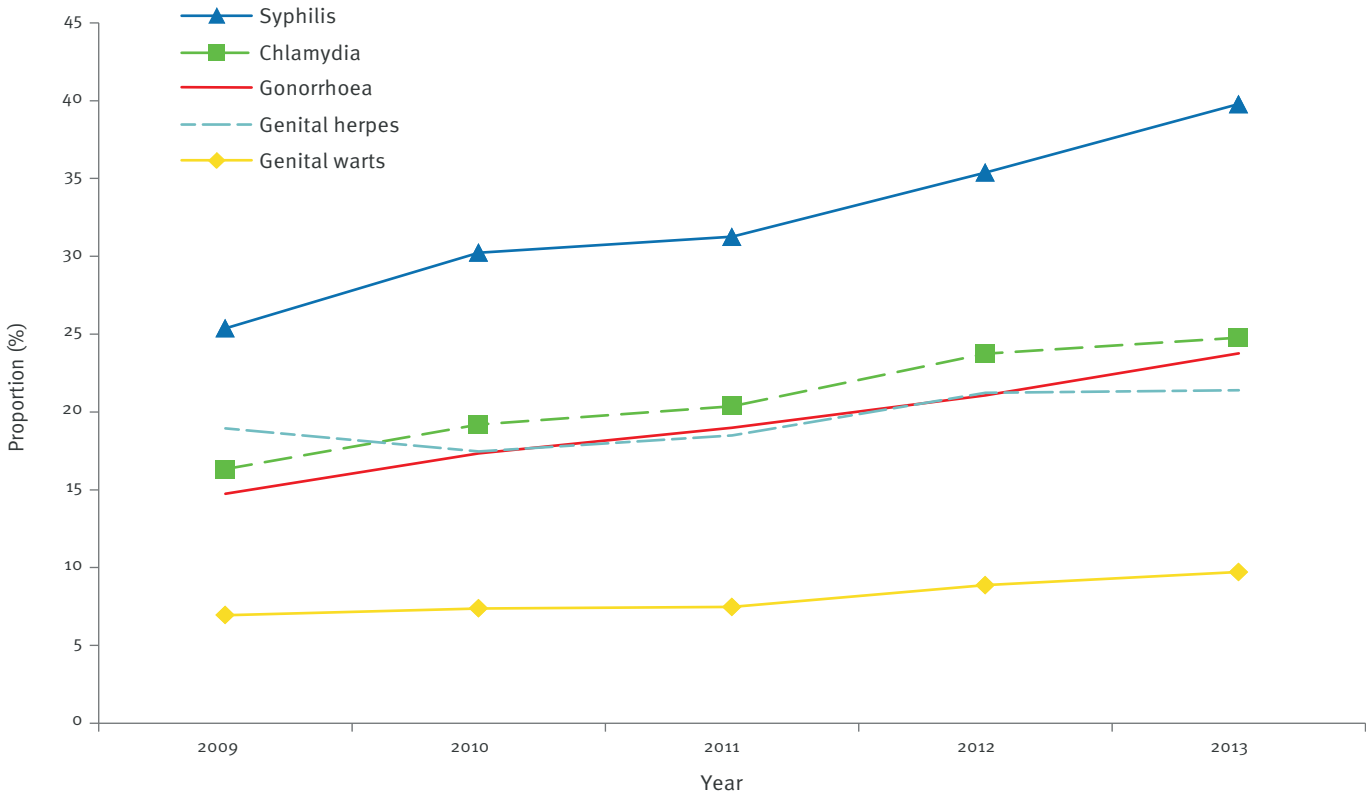
The rates of acute bacterial (gonorrhoea, chlamydia and syphilis) and acute viral STIs (first episode of genital warts and first episode of genital herpes) in HIV-positive and HIV negative/undiagnosed MSM were compared from 2009 to 2013. The numerators were individual HIV-positive and negative/undiagnosed MSM presenting at GUM clinics each year using data from GUMCADv2. The denominator for HIV-positive MSM was identified from SOPHID. The proportion of men aged 15 to 74 years who are MSM was estimated using data from Natsal-3. An estimated 2.6% of men in the UK had at least one male sexual partner in the past five years across all age groups of men [21]. This was applied to the mid-year population estimates from the ONS for the number of men aged 15 to 74 years for each year [22,23], and the estimated number of HIV-positive MSM was subtracted from this to calculate the denominator for HIV-negative/undiagnosed MSM. The results of a sensitivity analysis (data not shown) showed a small effect when using the upper and lower limits of the confidence interval (2.1% and 3% respectively) of the estimation of men in the UK having at least one male sexual partner in the past five years across all ages of men. For the most recent year of analysis, the range for bacterial STIs in HIV-negative MSM was 33 per 1,000 to 48 per 1,000.

Associations between sexually transmitted infection outcomes and HIV status

Univariate and multivariate logistic regression models were prepared for the MSM population attending GUM clinics in England for each individual MSM diagnosed with an acute bacterial STI (gonorrhoea, chlamydia and syphilis) for each year from 2009 to 2013 inclusive. Explanatory variables included all demographic variables from GUMCADv2 (age, ethnicity, continent of birth, and area of residence), diagnosed HIV status, and number of tests in the previous 12-month period

Figure 1

Proportion of acute sexually transmitted infection diagnoses in men who have sex with men which were in HIV-positive men who have sex with men, England, 2009–2013



for each respective bacterial STI; all were included in the final multivariate model.

Gonorrhoea and chlamydia re-infection rates by HIV status

The probability of patients who became re-infected with the most common bacterial STIs (gonorrhoea and chlamydia) within one year was estimated by the Kaplan-Meier method. Patients became at-risk from 42 days after the time of first attendance with gonorrhoea and chlamydia [24] and were censored at the end of the study period (31 December 2013). Data for calculating re-infection rates was obtained from GUMCADv2.

All statistical analyses were undertaken using Stata version 12 (StataCorp, College Station, Texas, US). P values‹0.05 were considered to be statistically significant.

Results

During the study period, the number of MSM attending GUM clinics recorded in GUMCADv2 increased from 78,226 in 2009 to 117,410 in 2013. The total number of MSM attendances increased from 241,676 to 316,250. The number of MSM in England estimated using Natsal-3 and ONS was 501,895 in 2009, increasing to 516,416 in 2013.

Acute sexually transmitted infections in known HIV-positive men who have sex with men

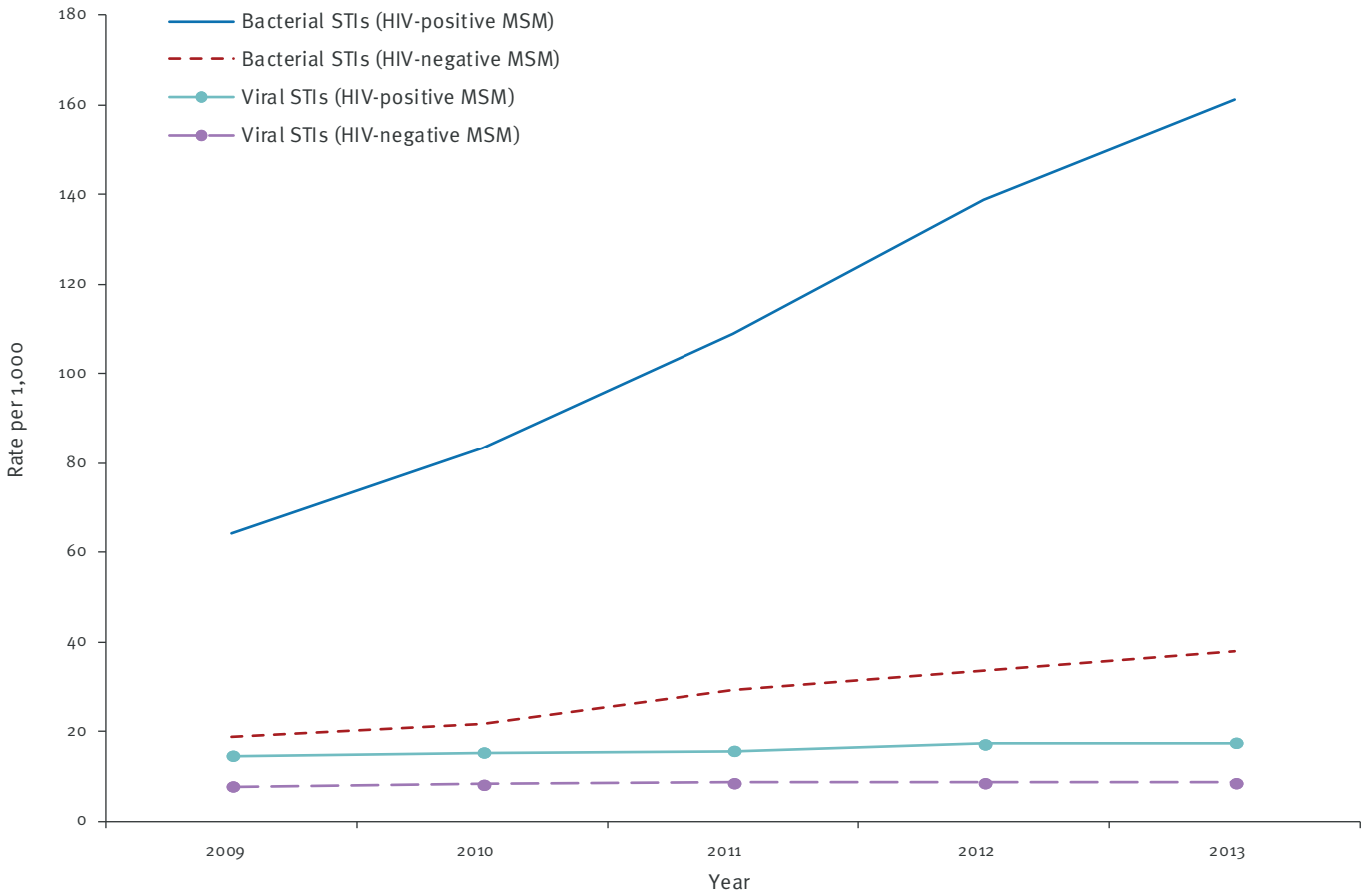
The proportion of acute STI diagnoses in MSM that were in HIV-positive MSM is shown in Figure 1. Overall, from 2009 to 2013, this proportion increased for all acute STIs: from 25% to 40% for syphilis, 16% to 25% for chlamydia, 15% to 24% for gonorrhoea, 19% to 21% for genital herpes and 7% to 10% for genital warts.

Sexually transmitted infection population rates in HIV-negative/undiagnosed and HIV-positive men who have sex with men

The rate of acute bacterial STIs in HIV-positive MSM nearly trebled (64 per 1,000 to 161 per 1,000), and increased from 3.2 times higher than the rate in HIV-negative/undiagnosed MSM in 2009 to 4.2 times higher in 2013 (Figure 2). For HIV-negative/undiagnosed MSM, the rate of acute bacterial STIs also increased to a lesser degree (19 per 1,000 to 38 per 1,000). The rate of acute viral STIs in HIV-positive MSM was approximately twice that observed in HIV-negative/undiagnosed MSM and remained fairly stable over the five year period (15 to 18 per 1,000 in HIV-positive and 8 to 9 per 1,000 in negative/undiagnosed MSM). This indicates that the rate of acute STIs in HIV-positive MSM was close to one in five (179 per 1,000).

Figure 2

Rates of acute bacterial and acute viral sexually transmitted infections in HIV-positive and negative/undiagnosed men who have sex with men per 1,000 men who have sex with men, England, 2009–2013



MSM: men who have sex with men; STI: sexually transmitted infection.

Bacterial STIs: gonorrhoea, chlamydia and syphilis
Viral STIs: first episode of genital warts and first episode of genital herpes

Associations between sexually transmitted infection outcomes and HIV status

Table 1 shows the final multivariate logistic regression models for gonorrhoea, chlamydia and syphilis adjusted for all explanatory variables. Data are presented for the most recent available year only. Table 2 shows the change in the adjusted odds ratio over time by HIV status. When compared with HIV-negative/undiagnosed MSM, the adjusted odds ratio (aOR) of being diagnosed with gonorrhoea, chlamydia and syphilis was significantly higher in HIV-positive MSM in all years analysed and increased over time ($p<0.001$).

Gonorrhoea and chlamydia re-infection rates by HIV status

The estimated probability of gonorrhoea and chlamydia re-infection is shown in Figure 3. A total of 34,090 and 31,206 MSM diagnosed with gonorrhoea and chlamydia respectively were included. The probability of repeat infection with gonorrhoea was estimated at 36.6% in HIV-positive, 33.2% in newly diagnosed and 22.7% in HIV-negative/undiagnosed MSM at the end of the 5 year follow-up period. For chlamydia, the estimated probability of repeat infection was 31.6% in HIV-positive, 23.7% in newly diagnosed and 17.3% in HIV-negative/undiagnosed MSM over the same period.

Discussion

For the first time, we have estimated the relative contribution of HIV-positive MSM to STI transmission over time in England. Since 2009, an increasing proportion of STIs has been diagnosed in HIV-positive MSM, and currently, the population rate of acute bacterial STIs is up to four times that of HIV-negative or undiagnosed MSM. We estimate that almost one in five of all diagnosed HIV-positive MSM in England had an acute STI diagnosed in 2013. The odds of being diagnosed with gonorrhoea, syphilis and chlamydia were significantly higher in HIV-positive relative to HIV-negative/undiagnosed MSM and increased over time. Re-infection rates of bacterial STIs were also considerably higher in HIV-positive MSM over a five-year follow-up period, indicative of rapid transmission in more dense sexual networks.

Table 1

Unadjusted and adjusted odds ratio for gonorrhoea, chlamydia and syphilis diagnoses, men who have sex with men, England, 2013

Variable		Gonorrhoea			Chlamydia				Syphilis			
	Number (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p value	Number (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p value	Number (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p value
HIV												
Negative/unaware	9,566 (78.2)	1	1		6,575 (76.4)	1	1		1,400 (60.9)	1	1	
Positive	2,674 (21.8)	1.22 (1.16-1.27)	1.75 (1.67-1.84)	<0.001	2,027 (23.6)	1.34 (1.27-1.41)	1.79 (1.69-1.90)	<0.001	900 (39.1)	2.80 (2.57-3.05)	4.05 (3.70-4.45)	<0.001
IMD score												
1 (least deprived)	883 (7.2)	1	1		689 (8.0)	1	1		159 (6.9)	1	1	
2	1,201 (9.8)	1.02 (0.93-1.11)	0.92 (0.84-1.01)	0.078	1,012 (11.8)	1.10 (0.99-1.21)	1.06 (0.95-1.17)	0.3	222 (9.6)	1.05 (0.85-1.28)	0.96 (0.78-1.19)	0.728
3	1,992 (16.3)	1.15 (1.04-1.21)	0.96 (0.88-1.05)	0.367	1,481 (17.2)	1.09 (0.99-1.20)	1.00 (0.91-1.1)	0.95	396 (17.2)	1.27 (1.05-1.52)	1.09 (0.90-1.32)	0.364
4	4,179 (34.1)	1.47 (1.35-1.55)	1.09 (1.00-1.18)	0.045	2,746 (31.9)	1.24 (1.13-1.35)	1.07 (0.98-1.18)	0.12	803 (34.9)	1.57 (1.32-1.86)	1.22 (1.02-1.46)	0.032
5 (most deprived)	3,985 (32.6)	1.48 (1.37-1.60)	1.11 (1.03-1.20)	0.009	2,674 (31.1)	1.28 (1.17-1.39)	1.10 (1.00-1.20)	0.04	720 (31.3)	1.49 (1.25-1.77)	1.15 (0.96-1.37)	0.138
Region												
Not London	4,827 (39.4)	1	1		4,077 (47.4)	1	1		999 (43.4)	1	1	
London	7,413 (60.6)	1.73 (1.66-1.80)	1.71 (1.64-1.78)	<0.001	4,525 (52.6)	1.25 (1.19-1.31)	1.21 (1.15-1.27)	<0.001	1,301 (56.6)	1.47 (1.35-1.59)	1.29 (1.18-1.42)	<0.001
Ethnic group												
White	9,684 (79.1)	1	1		6,724 (78.2)	1	1		1,778 (77.3)	1	1	
Black African	195 (1.6)	1.20 (1.04-1.40)	0.91 (0.77-1.08)	0.29	134 (1.6)	1.19 (1.00-1.42)	1.02 (0.84-1.25)	0.83	35 (1.5)	1.18 (0.84-1.65)	1.03 (0.70-1.50)	0.884
Black Caribbean	304 (2.5)	1.49 (1.32-1.69)	1.08 (0.95-1.23)	0.233	211 (2.5)	1.49 (1.29-1.73)	1.22 (1.05-1.42)	0.01	60 (2.6)	1.61 (1.24-2.09)	1.01 (0.76-1.33)	0.969
Black other	97 (0.8)	1.18 (0.96-1.47)	0.89 (0.71-1.10)	0.274	70 (0.8)	1.23 (0.96-1.58)	1.05 (0.82-1.35)	0.69	30 (1.3)	2.00 (1.38-2.89)	1.51 (1.03-2.21)	0.034
Asian or Asian British	414 (3.4)	0.87 (0.78-0.96)	0.76 (0.68-0.85)	<0.001	336 (3.9)	1.02 (0.91-1.14)	0.86 (0.75-0.98)	0.02	88 (3.8)	1.01 (0.81-1.25)	1.01 (0.79-1.29)	0.963
Mixed	501 (4.0)	1.33 (1.21-1.46)	1.03 (0.94-1.14)	0.517	337 (3.9)	1.29 (1.15-1.44)	1.12 (0.99-1.26)	0.06	88 (3.8)	1.27 (1.02-1.58)	1.08 (0.86-1.35)	0.507
Other ethnic	499 (4.1)	1.07 (0.97-1.17)	0.91 (0.82-1.01)	0.078	409 (4.7)	1.26 (1.13-1.40)	1.07 (0.95-1.21)	0.24	95 (4.1)	1.11 (0.90-1.36)	0.91 (0.72-1.15)	0.427
Unknown	546 (4.5)	0.90 (0.82-0.98)	1.00 (0.91-1.09)	0.93	381 (4.4)	0.90 (0.81-1.00)	0.97 (0.87-1.09)	0.64	126 (5.5)	1.13 (0.94-1.35)	1.23 (1.02-1.48)	0.033
Continent of birth												
Europe	9,636 (78.7)	1	1		6,687 (77.7)	1	1		1,746 (75.9)	1	1	
Africa	385 (3.2)	1.17 (1.05-1.32)	1.03 (0.91-1.17)	0.608	265 (3.1)	1.16 (1.02-1.32)	1.04 (0.9-1.2)	0.61	69 (3.0)	1.16 (0.91-1.47)	0.91 (0.69-1.19)	0.484
Asia	493 (4.0)	0.93 (0.85-1.02)	0.88 (0.78-0.98)	0.026	453 (5.3)	1.23 (1.11-1.36)	1.19 (1.05-1.35)	0.01	99 (4.3)	1.03 (0.84-1.26)	1.02 (0.79-1.30)	0.901
Australasia	251 (2.1)	1.39 (1.21-1.58)	1.15 (1.00-1.32)	0.044	165 (1.9)	1.31 (1.12-1.54)	1.24 (1.05-1.46)	0.01	32 (1.4)	0.97 (0.68-1.39)	0.84 (0.59-1.21)	0.346
North America	221 (1.8)	1.19 (1.03-1.36)	1.04 (0.90-1.20)	0.363	130 (1.5)	1.00 (0.84-1.20)	0.98 (0.81-1.17)	0.8	28 (1.2)	0.83 (0.57-1.21)	0.76 (0.52-1.11)	0.159
South America	594 (4.8)	1.46 (1.34-1.60)	1.07 (0.97-1.18)	0.153	390 (4.5)	1.38 (1.24-1.54)	1.1 (0.98-1.23)	0.11	162 (7.0)	2.20 (1.87-2.59)	1.53 (1.27-1.84)	<0.001
Unknown	660 (5.4)	0.87 (0.80-0.95)	0.83 (0.76-0.90)	<0.001	512 (6.0)	0.97 (0.89-1.07)	0.93 (0.85-1.03)	0.17	164 (7.1)	1.19 (1.01-1.40)	0.98 (0.83-1.16)	0.842
Number of tests for STI in past 12 months												
1	5,314 (43.4)	1	1		3,803 (44.2)	1	1		1,301 (56.6)	1	1	
2-4	4,854 (39.7)	1.62 (1.55-1.69)	1.56 (1.5-1.63)	<0.001	3,448 (40.1)	1.61 (1.53-1.69)	1.56 (1.48-1.63)	<0.001	906 (39.4)	1.23 (1.13-1.35)	1.14 (1.04-1.24)	0.004
>5	2,072 (16.9)	0.61 (0.58-0.65)	0.56 (0.53-0.59)	<0.001	1,351 (15.7)	0.56 (0.52-0.60)	0.48 (0.45-0.52)	<0.001	93 (4.0)	0.11 (0.09-0.14)	0.07 (0.05-0.08)	<0.001
Age group												
15-24 years	2,706 (22.2)	1	1		1,676 (19.6)	1	1		264 (11.5)	1	1	
25-34 years	5,274 (43.2)	1.11 (1.06-1.17)	0.94 (0.89-0.99)	0.019	3,282 (38.3)	1.12 (1.05-1.19)	1.02 (0.96-1.08)	0.57	766 (33.4)	1.66 (1.44-1.91)	1.37 (1.18-1.58)	<0.001
35-44 years	2,735 (22.4)	0.84 (0.79-0.89)	0.68 (0.64-0.72)	<0.001	2,134 (24.9)	1.06 (0.99-1.13)	0.93 (0.87-1)	0.04	701 (30.5)	2.21 (1.92-2.55)	1.61 (1.39-1.87)	<0.001
45-64 years	1,434 (11.7)	0.49 (0.46-0.53)	0.43 (0.40-0.46)	<0.001	1,388 (16.2)	0.77 (0.72-0.83)	0.71 (0.66-0.77)	<0.001	546 (23.8)	1.93 (1.66-2.24)	1.51 (1.29-1.76)	<0.001
>65 years	65 (0.5)	0.22 (0.16-0.27)	0.21 (0.16-0.27)	<0.001	89 (1.0)	0.47 (0.37-0.60)	0.47 (0.38-0.59)	<0.001	19 (0.8)	0.63 (0.40-1.01)	0.63 (0.39-1.00)	0.052

CI: confidence interval; IMD: Index of Multiple Deprivation; OR: odds ratio; STI: sexually transmitted infection.

Data restricted to men who have sex with men resident in England

Table 2

Adjusted odds ratios for gonorrhoea, chlamydia and syphilis diagnoses by HIV status in men who have sex with men, England, 2009–2013

Year	2009			2010			2011			2012			2013		
	Number (%)	Adjusted OR (95% CI)	p value	Number (%)	Adjusted OR (95% CI)	p value	Number (%)	Adjusted OR (95% CI)	p value	Number (%)	Adjusted OR (95% CI)	p value	Number (%)	Adjusted OR (95% CI)	p value
Gonorrhoea															
HIV neg	3,062 (86.0)	1		4,102 (83.0)	1		6,073 (82.8)	1		8,027 (80.1)	1		9,566 (78.2)	1	
HIV pos	497 (14.0)	1.43 (1.29–1.59)	<0.001	840 (17.0)	1.45 (1.34–1.58)	<0.001	1,258 (17.2)	1.44 (1.34–1.54)	<0.001	1,994 (19.9)	1.61 (1.52–1.70)	<0.001	2,674 (21.8)	1.75 (1.67–1.84)	<0.001
Chlamydia															
HIV neg	3,684 (84.1)	1		4,413 (81.6)	1		5,923 (81.4)	1		6,131 (77.2)	1		6,575 (76.4)	1	
HIV pos	697 (15.9)	1.5 (1.37–1.65)	<0.001	998 (18.4)	1.48 (1.37–1.59)	<0.001	1,356 (18.6)	1.44 (1.35–1.54)	<0.001	1,807 (22.8)	1.80 (1.70–1.91)	<0.001	2,027 (23.6)	1.79 (1.69–1.90)	<0.001
Syphilis															
HIV neg	1,271 (74.5)	1		1,171 (69.7)	1		1,385 (69.6)	1		1,370 (64.9)	1		1,400 (60.9)	1	
HIV pos	436 (25.5)	2.71 (2.41 – 3.05)	<0.001	509 (30.3)	2.74 (2.44–3.07)	<0.001	606 (30.4)	3.09 (2.78–3.43)	<0.001	742 (35.1)	3.66 (3.31–4.04)	<0.001	900 (39.1)	4.05 (3.70–4.45)	<0.001

CI: confidence interval; HIV neg: HIV negative/undiagnosed men who have sex with men; HIV pos: HIV-positive men who have sex with men; OR: odds ratio.
Data restricted to men who have sex with men resident within England

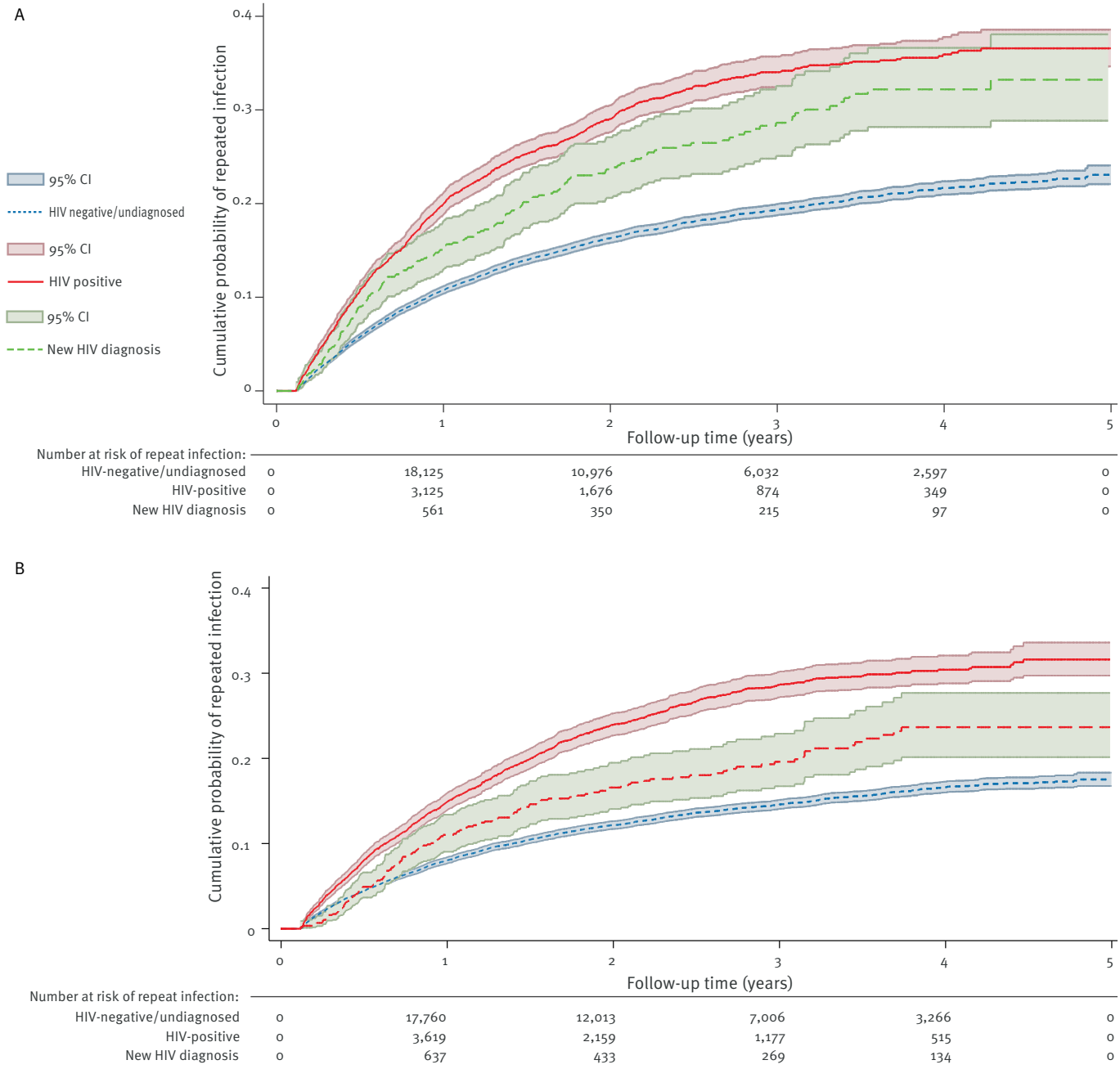
These findings strongly suggest that the sexual health of HIV-positive MSM in England is worsening. They are consistent with data from a cross-sectional survey of men in commercial gay venues in London, Brighton, Manchester, Glasgow and Edinburgh which demonstrated that numbers of STIs diagnosed in the previous 12 months were higher in MSM known to be HIV-infected compared with uninfected men (aOR 7.2, 95% CI 4.63–11.17) [25], and similar studies in Europe [26,27]. A study of LGV re-infection in the UK also found that, at baseline, repeaters were more likely to be HIV-positive compared with non-repeaters [28].

It seems probable that these changes in STI transmission patterns in HIV-positive MSM reflect increasing adoption of HIV seroadaptive behaviours and their impact on sexual network structures. HIV-positive MSM reporting seroadaptive behaviours are at higher risk of STIs compared with HIV-negative MSM [10-12]. One study reported that HIV-positive MSM practising seroadaptive behaviours had a threefold increased risk of bacterial STIs, with almost a third of HIV-positive MSM reporting an STI in the past year, compared with 9% of HIV-negative MSM [11]. However, despite the considerable changes in STI transmission patterns in HIV-positive MSM seen in our study, the degree to which transmission in HIV-positive MSM engaging in seroadaptive behaviours is fuelling current STI epidemics in England is unclear. The recent emergence of relatively rare infections such as LGV and S. flexneri in the UK has been strongly and predominantly associated with transmission in HIV-positive MSM [5,6,29]. Likewise for syphilis, our study showed that 39.1% of cases in MSM in England were known to be HIV-positive, and this is consistent with data from the United States, Australia and Europe [26,27,30,31]. The duration of infectiousness with Shigella, LGV and syphilis may be short as these infections are typically symptomatic, so it is highly likely that their transmission is being sustained in highly active sexual networks of HIV-positive MSM engaging in seroadaptive behaviours [32]. However, fewer than 25% of MSM diagnosed with chlamydia and gonorrhoea (and even less with viral STIs) in our study were HIV-positive. Therefore, while seroadaptive behaviours in HIV-positive MSM may be making an important contribution to the transmission of chlamydia, gonorrhoea and viral STIs in MSM, they are not necessary to sustain infection at endemic levels in the wider MSM population.

HIV seroadaptive behaviours will likely have other negative or unintended consequences for the sexual health of MSM. The presence of an STI may compromise the health of HIV-positive MSM through several mechanisms including a reduction in CD4 cell count as well as acute increases in HIV viral load, which may compromise effective antiretroviral therapy [33-35]. In addition, STIs may also increase HIV infectiousness by facilitating HIV shedding in the genital tract or rectal mucosa [36]. Further, evidence suggests that a low viral load may reduce the probability of infecting

Figure 3

Estimated probability of repeat gonococcal infection (A) and of repeat chlamydial infection (B) in men who have sex with men attending genitourinary medicine clinics by HIV co-infection, England, 2009–2013



a sexual partner [37-39], thus, HIV-positive MSM may engage in seroadaptive behaviours when they receive highly active antiretroviral therapy (HAART) or have an undetectable viral load. However, surveys of gay commercial venues and gyms in London, Glasgow and Edinburgh suggest the proportion of MSM reporting unprotected anal intercourse with partners of unknown or discordant HIV status has increased, leading to risk of HIV as well as other STI transmission [8,14].

A study by Fox et al. showed significant reduction in self-reported HIV transmission-risk behaviour in MSM recently diagnosed with HIV, with patients reporting greater condom use and fewer sexual partners [40]. However, these may have limited impact on STI incidence due to the various routes of transmission of STIs (such as oral, digital and use of sex toys). Furthermore, in MSM recently diagnosed with HIV, those reporting continued transmission-risk behaviour were more likely to have another STI [40]. Thus, health promotion activities should also consider the broader context around sexual risk-taking in MSM, especially in those diagnosed with HIV. The recent Public Health England framework for promoting the health and well being of MSM highlighted the interaction of mental health, alcohol and drug use, and sexual risk behaviour [41]. There is increasing concern on the interaction between drug use and STIs, especially in HIV-positive

MSM, and that in developing appropriate interventions and services, the specific needs of HIV-positive MSM should be considered [29]. Furthermore, the high incidence of asymptomatic STIs, especially in extra-genital sites [42,43] emphasises the need to promote regular screening for STIs in HIV-positive individuals [44,45]. Nonetheless, surveys of healthcare providers in the US have reported significant barriers, especially in screening for gonorrhoea and chlamydia, which include time constraints, difficulty obtaining a sexual history, language and cultural barriers, and patient confidentiality concerns [46].

There are several limitations of this study. There may be a degree of ascertainment bias in the assessment of HIV status in MSM in patients with a longer history in GUMCADv2. However, sensitivity analysis (data not shown) was performed by identifying HIV-positive MSM from a retrospective review of a single year of GUMCADv2 data, and there was only a minimal impact on the results. The probability of repeat infection may also have been underestimated as, in this analysis, repeat diagnosis was used as a proxy measure for repeat infection. Some patients will have become re-infected but will remain undiagnosed, as only patients who returned to the same clinic for testing were assessed in the analysis. This is a limitation of GUMCADv2, as it allows only longitudinal patient data within a particular clinic or service and attendances by the same patient at different clinics cannot be monitored [19]. However, the data quality and completeness of GUMCADv2 is extremely high with 100% submissions from GUM clinics [19]. HIV-positive MSM engaged in care are also more likely to return regularly for STI screening during clinic visits and this may have contributed to the proportion and rates of STIs observed. Diagnosis of STIs (including HIV) is dependent on screening practices and frequency of screening. It is therefore not a true measure of incidence of infection but provides a good proxy for infection. A further limitation is the estimation of the true size of the MSM population in the UK. However, the methodology employed in Natsal-3 is among the most robust to estimate the size of this population. Furthermore, between Natsal-2 and Natsal-3, there was no significant increase in the proportion of men reporting same sex partners in the past 5 years [21]. Thus, the results of this longitudinal data analysis provide valuable insights into the complexity and evolution of STI epidemics in England.

The presence of an increasing proportion and rates of acute STIs in HIV-positive MSM, a population which also has higher rates of repeat infection and reports higher risk sexual behaviour, presents an increased risk for the sexual health of all MSM. This therefore merits public health action through improved monitoring and intervention. Currently, the collection of behavioural data is being piloted alongside that of clinical and socio-demographic data and this will allow further insights into the impact of seroadaptive practices to be explored in the future. Improved public health interventions with a holistic approach focussing on promoting condom use, reducing high risk behaviour and increasing the frequency of STI testing in MSM should be a priority.

Conflict of interest

None declared.

Authors' contributions

Gwenda Hughes and Anthony Nardone devised the study, advised on data analysis and participated in interpreting the data. Ramona Malek, Holly Mitchell and Martina Furegato carried out statistical analysis, participated in data analysis and intepreting the data. Ian Simms and Hamish Mohammed participated in interpreting the data. Ramona Malek prepared the first draft of the manuscript. All authors contributed to the final manuscript.

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Internet-based recruitment system for HIV and STI screening for men who have sex with men in Estonia, 2013: analysis of preliminary outcomes

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The aim of the current project was to develop an Internet-based recruitment system for HIV and sexually transmitted infection (STI) screening for men who have sex with men (MSM) in Estonia in order to collect biological samples during behavioural studies. In 2013, an Internet-based HIV risk-behaviour survey was conducted among MSM living in Estonia. After completing the questionnaire, all participants were offered anonymous and free-of-charge STI testing. They could either order a urine sample kit by post to screen for chlamydia infections (including lymphogranuloma venereum (LGV)), trichomoniasis, gonorrhoea and *Mycoplasma genitalium* infections, or visit a laboratory for HIV, hepatitis A virus, hepatitis B virus, hepatitis C virus and syphilis screening. Of 301 participants who completed the questionnaire, 265 (88%), reported that they were MSM. Of these 265 MSM, 68 (26%) underwent various types of testing. In the multiple regression analysis, Russian as the first language, previous HIV testing and living in a city or town increased the odds of testing during the study. Linking Internet-based behavioural data collection with biological sample collection is a promising approach. As there are no specific STI services for MSM in Estonia, this system could also be used as an additional option for anonymous and free-of-charge STI screening.

Background

Men who have sex with men (MSM) continue to be one of the groups at highest risk for HIV and sexually transmitted infections (STI) in the European Union. MSM made up the highest proportion of total number of HIV cases in Europe in 2013 (42%), and in 2012 more than a third of reported gonorrhoea cases in Europe were in MSM (38%) [1,2].

In 2013, Estonia had a total population of around 1.3 million, and 24.6 newly diagnosed HIV cases and 1.8 AIDS cases per 100,000 population [3]. It has been estimated that there are about 9,000 MSM in Estonia [4]. Triangulation of data from various studies suggests that HIV prevalence in MSM could be around 2–3% [5]. No data are available on STI prevalence in MSM or the proportion of reported STI cases that are in MSM.

Gathering accurate data on HIV prevalence and risk behaviours in MSM has posed a challenge for researchers in Estonia [6]. For HIV-prevalence estimations, 59 MSM were recruited by using respondent-driven sampling (RDS) [6] and 79 by convenience sampling in gay venues and community-based organisations [7]. These sampling methods did not yield the desired sample size. At the same time, MSM participation in four consecutive Internet studies (2004, 2006, 2007 and 2010) has been relatively high, especially in the European MSM Internet Study (EMIS) [8–11]. Unfortunately, the Internet does not offer the opportunity to gather biological material for testing to estimate HIV/STI prevalence rates.

In other countries, studies of MSM as well as of the general population have shown that Internet-based screening and self-sampled postal testing for STIs is an effective, acceptable and feasible approach [12–16]. Our aim was to develop an Internet-based recruitment system for HIV and STI screening for MSM in order to collect biological samples during behavioural studies.

Methods

We conducted an Internet-based study of MSM to investigate sexual and drug-use behaviours, previous HIV/STI testing, mental health, internalised homonegativity and HIV/STI related knowledge and attitudes among this population group. The eligibility criteria included: self-identifying as male; living in Estonia; age of 18 years or older; and being sexually attracted to men and/or having ever had sex with a man. Taking into account the range of response rates in previous studies, the planned sample size was 300 [8–11].

Questionnaire

The questionnaire was constructed using Internet survey software (http://www.limesurvey.org/). The questionnaire was presented over 63 web pages and included 144 questions. It took around 45 minutes to complete. To minimise completion time, it was tailored with intra-questionnaire filters. For example, specific questions regarding HIV testing and treatment were not shown if the participant had already stated that they had never been tested for HIV or were HIV-negative. The questionnaire was accessible online from April to September 2013. All study materials were available in both Estonian and Russian (25% of the population of Estonia is predominantly Russian-speaking [17]). The questionnaire's design was based on previous Estonian and international experiences [7–11, 18] and included the following domains:

- Sociodemographic data.
- Sexual orientation (homosexual, bisexual, straight, heterosexual, any other term (please specify) or 'I don't usually use a term/define myself'), type of relationship, and sexual behaviour.
- HIV and STI testing and history. To assess HIV testing history, we asked: 'Have you ever been tested for HIV?' and 'What was the result of your last HIV test?' To assess STI testing history, we asked: 'Have you ever been tested for any STI (for example syphilis, gonorrhoea, chlamydia, trichomoniasis, genital herpes)?'; 'Have you ever been diagnosed with any STI (for example syphilis, gonorrhoea, chlamydia, trichomoniasis, genital herpes)?'; and 'Have you ever had anal swabs taken for STI diagnosis?'
- Confidence about HIV and STI testing possibilities was assessed with the following two questions 'How confident are you that you could get an HIV test if you wanted one?' and 'How confident are you that you could get a test for STIs (other than HIV) if you thought you needed it?' [11]. Responses were indicated by using a four-point Likert-type scale (1=very confident, 4=not at all confident).
- Illegal drug use and alcohol use (CAGE questionnaire) [19]. The CAGE questionnaire is widely used to screen patients with alcohol abuse or dependence in the general population as well as in clinical samples. It includes four yes/no items. Subjects who responded affirmatively to two or more questions were classified as CAGE-positive (problem drinkers with high likelihood of the presence of alcoholism).
- Internalised homonegativity. We used a short form of the 'Reactions to Homosexuality' scale [20, 21] that included seven of the original items loading on three factors: personal comfort with a gay identity, social comfort with gay men, and public identification as gay. Responses were indicated by using a seven-point Likert-type scale (0=strongly disagree, 6=strongly agree). All the items were coded at analysis so that a higher score indicated higher internalised homonegativity. The scale was additive, ranging from 0 to 6.
- Contacts with HIV prevention services, HIV/STI knowledge and attitudes to HIV, STIs and related issues.

Recruitment and promotion

The study was promoted through Estonia-based gay online social media, gay community organisations, the national network of anonymous HIV testing sites and youth counselling centres. A special Facebook page was created to promote the study. The English version of the slogan of the study was 'Good health: the pride of every man!' Advertisements directed users to the opening page of the study. The opening page described the study aims and informed potential participants that their data would be anonymous, that no IP addresses were saved, and that the survey software installed no cookies or other trace files on computers. The participants could not pause the process of filling in the questionnaire and sign in later to finish it. Not collecting IP addresses meant that it was possible for one person to submit two or more questionnaires.

Testing for HIV and STIs and reporting of the results

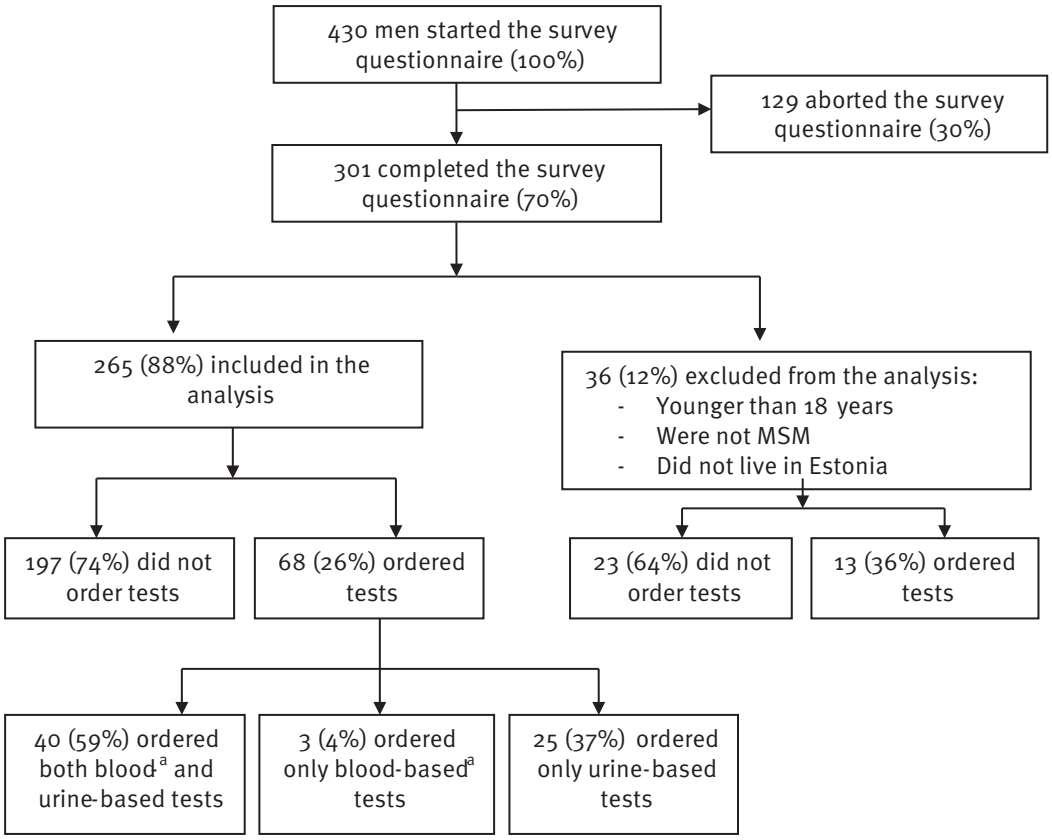
All the participants were offered voluntary, anonymous and free-of-charge HIV and STI testing for HIV, hepatitis C virus (HCV), hepatitis B virus (HBV), hepatitis A virus (HAV) and syphilis markers from blood, and for *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, *Chlamydia trachomatis* (including lymphogranuloma venereum (LGV) genotyping) and *Mycoplasma genitalia* from urine sample.

After submitting the questionnaire, participants were referred to a landing page where each participant was assigned a unique study participation code (for example, u_aa1234) and detailed information, how to get tested and how the data were protected. For testing we used a special web-based testing service called *Testikodus* ('Test at Home' in English). This is an Internet portal run by Quattromed HTI Laborid OÜ (QM), which is the largest medical laboratory in Estonia. The portal offers anonymous fee-based testing for STIs. For the purposes of our study we created a special pathway for those who had filled in the study questionnaire to order test kits free of charge. There were two options to get tested and receive test results:

1. For blood-based testing (HIV, HCV, HBV, HAV and syphilis) the participants had to visit the QM laboratory in person (six sites in larger cities across Estonia, ranging from the capital city Tallinn (population 406,000, 2013) to Võru (population 12,800, 2013) [17]). The test results were available within five working days and could be received only by visiting the laboratory. Those who went to the laboratory could either return the urine sample kit by post or take the urine sample to the laboratory, depending on their preference.

Figure

Participant flow chart and drop-out in various stages of the project, Internet study of men who have sex with men, Estonia, 2013



MSM: men who have sex with men.

Percentages are calculated on the basis of the previous cell

[a] Required a visit to the laboratory

2. For urine-based testing (gonorrhoea, trichomoniasis, chlamydia, LGV, and mycoplasmosis) the participants could order the urine sample kit to be delivered by SmartPOST courier services. For this they had to create an account in the *Testikodus* website using their unique study participation code. Participants were asked to give their email address and/or phone number, which were needed for the SmartPOST courier services. Through this account and emails the participants received confirmation once their order was successfully placed and the test results were ready. The test results were available within five working days and could be received through the *Testikodus* website account.

Testing could be carried out until 31 December 2013 in order to be included in the study.

If a participant tested positive for any of the urine-based tests, he was given information about where to go for treatment. Participants could attend one sexual health clinic in Tallinn anonymously and get treatment free of charge on presentation of the unique study participation code. If a participant tested positive for any of the blood-based tests, it was explained in the laboratory that these were screening tests and that the participant should go to an infectious diseases doctor for further tests to confirm the diagnosis. Due to the anonymous nature of the study we were not able to find out how many participants accessed confirmatory testing.

Laboratory testing

Ten ml of venous blood and/or 20 ml of first void urine were collected from the participants. The following methods were used for infectious marker testing:

- HIV-antibodies and antigen (HIV 1,2 Ab+Ag), HCV-antibodies (HCV Ab), anti-HAV IgM/IgG, HBsAg, and syphilis antibodies: chemiluminescence.
- Chlamydia (*C. trachomatis*, including LGV serovar), gonorrhea (*N. gonorrhoeae*), trichomoniasis (*T. vaginalis*) and mycoplasmosis (*M. genitalium*): PCR.

Data management and statistical analysis

The data from the questionnaire and the unique participation codes (created in the *Testikodus* website and linked to the test results) were stored in different databases. The data were linked manually based on the date and time of day (e.g 10.07.2014 22:34) the participant submitted the questionnaire, and the date and time he reached the landing page (time difference approximately one second). The personal data necessary for ordering test kits (mobile phone numbers, email addresses, etc) were stored only on the *Testikodus* database and never linked to the data from anonymous questionnaires.

The statistical analyses were performed with Stata 11.0 (StataCorp LP, College Station, TX). Descriptive statistics were used to characterise participants. The dependent variable in our analyses was the fact of ordering either blood or urine-based tests. The associations between the participant's characteristics and dependent variables were evaluated using a Wilcoxon rank-sum test, a Fisher's exact test, or a one-way analysis of variance (ANOVA), followed by univariate and multivariable logistic regressions. For multivariable logistic regression, testing during the study was adjusted for age and factors significantly associated in the univariate analysis (at $p<0.05$).

Ethical issues

The study was approved by the Tallinn Medical Research Ethics Committee. Before answering the questions, all participants were required to indicate that they understood the aims and methods of the study and that they consented to take part in it. The opening and landing pages included contact information for the principal investigator in case anybody had any further questions related to the study aims and procedures.

Results

Overall, 430 people began the questionnaire. Of these, 70% of them (n=301) completed the questionnaire and submitted their answers, and 30% (n=129) broke off or did not submit at the end of the questionnaire. Those who completed the questionnaire were compared with those who did not for age, first language (Estonian vs Russian), region (city vs countryside) and satisfaction with their economic situation. The only statistically significant difference was related to region, with more people living in the countryside among those who broke off compared with those who completed the questionnaire (24% vs 13%; p=0.02).

Of the 301 participants who completed the questionnaire, 12% (n=36) did not meet the inclusion criteria (18 did not live in Estonia, 10 were not MSM, and eight were younger than 18 years of age). Thus the total sample size of MSM was 265. As our aim was to develop a testing system and recruit MSM, the analysis of factors related to testing during the study uses data only from those 265 men who were eligible. Participant flowchart and drop-out are presented in the Figure.

Participants

The characteristics of the MSM in the study are presented in Table 1. The median age was 31 years (mean age 33 years; range 18–67 years; 53% were older than 30 years), 90% completed the questionnaire in Estonian, 71% were from the capital city Tallinn and the surrounding area; 85% were working full- or part-time, 43% had higher education; 44% were in a steady relationship with a man or a woman; 76% considered themselves homosexual and 24% bisexual. A total of 98% had ever had sex, 33% were CAGE positive and 23% had used illegal drugs in the last 12 months). The mean internalised homonegativity score was 1.9 (SD 1.2; range 0.2–5.7).

Of the total sample, 70% had ever been tested for HIV, and 36% had been tested in the last 12 months. Self-reported HIV-prevalence was 4%.

Fifty-one per cent of the total sample had ever been tested for STIs, 19% in the last 12 months. 24% had ever been diagnosed with an STI. 8% of those who had ever been tested for STIs reported having had anal swabs taken.

30% of the total sample had received a full-course vaccination against hepatitis B, 3% had ever had hepatitis B. 18% of the MSM had received a full-course vaccination against hepatitis A, and 5% had ever had hepatitis A.

Testing

A total of 81 men were tested during the study (27% of all those who completed the questionnaire): 68 MSM (testing rate among MSM: 26%) and 13 non-eligible participants (testing rate among non-eligible participants: 35%) (Figure). 74 men (91%) were tested within one month of completing the questionnaire, three within two months (4%), and four within four months (5%).

Of the 68 MSM who were tested, 40 were tested for all infections (59%), three (4%) gave only blood and 25 provided only urine samples (37%). Thus a total of 65 provided urine samples (25% of MSM who completed the questionnaire), and 43 provided blood samples (16% of MSM who completed the questionnaire).

The univariate analysis identified several factors associated with testing among MSM during the study (Table 1). The multivariable logistic regression analysis showed that testing during the study was independently associated with Russian as the first language, living in towns/cities and having ever been tested for HIV (Table 1).

Test results

The test results are presented in Table 2. Of the 17 participants positive for HAV antibodies, two had had hepatitis A, five had been vaccinated against HAV, four had not been vaccinated and six did not know their

Table 1A

Participant characteristics, univariate and multivariable analysis of factors associated with biological testing, Internet study of men who have sex with men, Estonia, 2013 (n=265)

	Total n = 265	Testing during the study		Univariate odds ratio (95% CI)	Multiple regression	
		No n = 197	Yes n = 68		Adjusted odds ratio (95% CI)	p value
	N (%)	N (%)	N (%)			
Sociodemographics						
Age						
≤ 30 years	125 (47)	96 (77)	29 (23)	1.00	1.00	-
› 30 years	140 (53)	101 (72)	39 (28)	1.29 (0.73–2.23)	1.26 (0.67–2.27)	-
First language						
Estonian	238 (90)	185 (78)	53 (22)	1.00	1.00	-
Russian	27 (10)	12 (44.4)	15 (55.6)	4.36 (1.93–9.89)a	3.82 (1.61–9.08)	0.002
County[b]						
Tallinn/Harjumaa	186 (70)	129 (69)	57 (31)	1.00	-	-
Other	78 (29)	67 (86)	11 (14)	0.29 (0.14–0.59)a	-	-
Region						
Town	231 (87)	165 (71)	66 (29)	1.00	1.00	-
Countryside	34 (13)	32 (94)	2 (6)	0.16 (0.04–0.67)c	0.37 (0.18–0.76)	0.007
Education						
Primary/secondary	151 (57)	113 (75)	38 (25)	1.00	-	-
Higher	114 (43)	84 (74)	30 (26)	1.06 (0.61–1.85)	-	-
Occupation						
Working full- or part time	225 (85)	165 (73)	60 (27)	1.00	-	-
Other (retired, student, long-term sick leave, etc.)	40 (15)	32 (80.0)	8 (20)	0.69 (0.30–1.58)	-	-
Relationship type						
No regular partner	146 (55)	107 (73)	39 (27)	1.00	-	-
Male regular partner	92 (35)	69 (75)	23 (25)	0.91 (0.50–1.66)	-	-
Female regular partner	21 (8)	15 (71)	6 (29)	1.10 (0.40–3.03)	-	-
Sexual behaviour						
Condom use at last anal sex with a man (k29)						
No	112 (47)	79 (71)	33 (29)	1.00	-	-
Yes	126 (53)	95 (75)	31 (25)	0.78 (0.44–1.39)	-	-
Condom use last anal sex with a male casual partner (k45)						
No	64 (30)	41 (64)	23 (35.9)	1.00	-	-
Yes	151 (70)	111 (73)	40 (26.5)	0.64 (0.34–1.20)	-	-
Casual sex with a man in the last 12 months						
No	65 (28)	50 (77)	15 (23)	1.00	-	-
Yes	170 (72)	120 (71)	50 (29)	1.39 (0.71–2.70)	-	-
Unprotected anal sex with a man in the last 12 months						
No	83 (35)	65 (78)	18 (22)	1.00	-	-
Yes	155 (65)	109 (70)	46 (30)	1.52 (0.82–2.85)	-	-
Sex abroad ever						
No	116 (46.2)	89 (77)	27 (23)	1.00	-	-
Yes	135 (53.8)	96 (71)	39 (29)	1.34 (0.76–2.37)	-	-
Anal sex in a club ever						
No	140 (54)	108 (77)	32 (23)	1.00	-	-
Yes	118 (46)	82 (69)	36 (31)	1.48 (0.85–2.58)	-	-

CI: confidence intervals; SD: standard deviation; STI: sexually transmitted infection.

[a] p<0.001

[b] Was not included in multivariable regression analysis because it was highly correlated to region of living (which included both town and countryside)

[c] p<0.01

[d] Includes those who have never drunk alcoholic beverages (n=11; 4.2% of the participants)

[e] p<0.05

Table 1B

Participant characteristics, univariate and multivariable analysis of factors associated with biological testing, Internet study of men who have sex with men, Estonia, 2013 (n=265)

	Total n = 265	Testing during the study		Univariate odds ratio (95% CI)	Multiple regression	
		No n = 197	Yes n = 68			
	N (%)	N (%)	N (%)		Adjusted odds ratio (95% CI)	p value
Sexual behaviour						
Sex with a woman ever						
No	119 (46)	84 (71)	35 (29)	1.00	-	-
Yes	140 (54)	107 (76)	33 (24)	0.74 (0.43–1.29)	-	-
Sexual orientation						
Homosexual	192 (76)	139 (72)	53 (28)	1.00	-	-
Bisexual	61 (24)	49 (80)	12 (20)	0.64 (0.32–1.30)	-	-
Internalised homonegativity (mean, SD)	1.9 (SD 1.2; 95% CI 1.8–2.1)	1.9 (SD 1.2; 95% CI 1.7–2.1)	2.1 (SD 1.2; 95% CI 1.7–2.3)		-	-
Drug and alcohol use						
Illegal drug use in the last 12 months						
No	204 (77)	152 (75)	52 (25)	1.00	-	-
Yes	61 (23)	45 (74)	16 (26)	1.04 (0.54–1.99)	-	-
CAGE score [17]						
Negative (0–2)d	178 (67)	131 (74)	47 (26)	1.00	-	-
Positive (3–4)	87 (33)	66 (76)	21 (24)	0.89 (0.49–1.61)	-	-
HIV and STI testing and history						
Responses to 'How confident are you that you could get a test for HIV if you wanted one?'						
Not so confident	93 (35)	71 (76)	22 (24)	1.00	-	-
Very confident	172 (65)	126 (73)	46 (27)	1.18 (0.66–2.12)	-	-
Responses to 'How confident are you that you could get a test for STIs (other than HIV) if you wanted one?						
Not so confident	130 (50)	97 (75)	33 (25)	1.00	-	-
Very confident	135 (51)	100 (74)	35 (26)	1.03 (0.59–1.79)	-	-
STI test ever						
No	126 (49)	100 (79)	26 (21)	1.00	-	-
Yes	132 (51)	93 (71)	39 (30)	1.61 (0.91–2.85)	-	-
STI test in last 12 months						
No	216 (82)	166 (7)	50 (23)	1.00	-	-
Yes	49 (18)	31 (63)	18 (37)	1.93 (0.99–3.73)	-	-
STI ever						
No	202 (76)	153 (76)	49 (24)	1.00	-	-
Yes	63 (24)	44 (70)	19 (30)	1.35 (0.72–2.52)	-	-
HIV test ever						
No	79 (30)	67 (85)	12 (15)	1.00	1.00	-
Yes	185 (70)	129 (70)	56 (30)	2.4 (1.22–4.83)e	2.38 (1.15–4.94)	0.02
HIV test in last 12 months						
No	168 (63)	130 (77)	38 (23)	1.00	-	-
Yes	97 (37)	67 (69)	30 (31)	1.53 (0.87–2.69)	-	-

CI: confidence intervals; SD: standard deviation; STI: sexually transmitted infection.

[a] p<0.001

[b] Was not included in multivariable regression analysis because it was highly correlated to region of living (which included both town and countryside)

[c] p<0.01

[d] Includes those who have never drunk alcoholic beverages (n=11; 4.2% of the participants)

[e] p<0.05

Table 2

Results of biological testing, Internet study of men who have sex with men, Estonia, 2013 (n=265)

	Positive		Negative		Total number of tests
	N	%	N	%	N
Chlamydia trachomatis LGV	-	-	65	100	65
C. trachomatis	1	2	64	98	65
Mycoplasma genitalium	-	-	65	100	65
Neisseria gonorrhoeae	1	2	64	98	65
Trichomonas vaginalis	-	-	65	100	65
Treponema pallidum (antibodies)	2	5	41	95	43
HAV antibodies	17	40	26	60	43
HBsAg	-	-	43	100	43
HCV antibodies	2	5	41	95	43
HIV 1/2 antigen + antibodies	3	7	40	93	43

LGV: lymphogranuloma venereum; HAV: hepatitis A virus; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus.

vaccination status. HAV antibody prevalence among non-vaccinated men was 32% (11/34). Neither of the two participants who tested positive for HCV antibodies had been aware of their status; one had had blood transfusion before 1994 and one had injected drugs in the past. Three people were HIV-positive, two of whom were already aware of their status. The third man had considered himself HIV-negative, and had last been tested for HIV less than a year previously. As he was willing to provide his personal data for the laboratory (which was not mandatory), his test result was confirmed and he was linked to HIV care in Tallinn.

Discussion

This was the first attempt in Estonia to collect biological samples for blood-borne and STI marker detection from MSM participating in an Internet-based behavioural study. We recruited 265 MSM, of whom 26% underwent various types of testing. We detected 4 STI cases, and one new HIV case.

Of the people who began the questionnaire, 30% broke off before the end. We presume this was most likely due to the length of the questionnaire. To improve this in the future, we will shorten the questionnaire considerably. Those who broke off the questionnaire were more likely to be living in the countryside. One reason may have been perceived difficulties in accessing the testing offered during the study. People living in smaller communities may also have been more worried about confidentiality when ordering the test kits by post.

The overall sample size was smaller compared with EMIS 2010, but more or less comparable to the earlier Internet studies [8–11]. Table 3 presents the main sociodemographic and HIV-testing-related data from the previous studies. Our sample appears to be less diverse compared with previous Internet studies, which recruited a larger proportion of MSM who were bisexual, non-Estonian and lived outside the capital city Tallinn and the surrounding Harju county. The mean age of the participants in different studies has increased somewhat as well as the proportion ever tested for HIV (which may be related to vigorous HIV testing campaigns targeting MSM in recent years).

According to Statistics Estonia, 79% of households in Estonia had access to the Internet at home in 2013 (82% of those living in towns and 73% of those living in the countryside). This has improved considerably since 2005 when the respective percentage was 37% (32% living in towns and 24% living in the countryside) [17]. We do not have specific data about Internet access among MSM, but we assume it is at least as good as among the general population. Thus the reason for lower sample size is not related to the decreased access to the Internet.

The way in which the survey was promoted may be one of the reasons for the smaller and less diverse sample. With EMIS 2010, for example, the largest recruiters were not national websites but pan-European websites that sent instant messages (IMs) to their members, and 24% of the Estonian participants in EMIS were recruited through IMs sent by PlanetRomeo [11], which we did not use this time. In 2010, 12 national websites were used for promotion, but this time only 11 were used, only one of which was primarily Russian-language. In the future, participation rates could be improved by better promotion.

Twenty-six per cent of participants were tested for STIs or bloodborne infections. In a population-based survey conducted in Estonia to estimate the prevalence of

Table 3

Comparison of sample size, and selected sociodemographic, HIV testing, and HIV prevalence data from studies of men who have sex with men in Estonia, 2004–2013

Study type	2004 [7]	2006 [8]	2007 [9]	2007 [16]	2008 [6]	2010 [10]	2013
	Internet	Internet	Internet	RDS	Venue-based	Internet	Combination
Number of participants who completed the questionnaire	358	331	399	NA	NA	629	301
Final eligible sample size, n (%)	312 (87%)	232 (70%)	361 (90%)	59	79	594 (94%)	265 (88%)
Mean age of the participants, years	28	27	31	27	30[a]	32	33
Percentage homosexual	59	66	67	68	55	65	76
Percentage with higher education	38	43	40	54	51	45	43
Percentage of Estonians	76	60	79	53	71	85	90
Percentage living in Tallinn and Harju county	62	59	66	100	100	60	71
Percentage HIV-tested ever during lifetime (%)	41	47	50	71	68	60	70
Self-reported HIV-prevalence, n (%)	NA	NA	NA	NA	1 (1.3%)[b]	10 (1.7%)[b]	8 (3.0%)[b]
HIV-prevalence during the study, n (%)	NA	NA	NA	1 (1.7%)[b]	2 (2.5%)[b]	NA	3/43 (7.0%)

RDS: respondent-driven sampling; NA: not available.

[a] Median age

[b] Among all participants eligible for the study

C. trachomatis infection (tests were collected by participants and returned by post) the overall response rate for men was 32% [22]. In a systematic review of strategies for home-based chlamydia and gonorrhoea screening, the median specimen return rate for postal test kits requested through the Internet or telephone was 32% (27–47%) for the general population [15].

STI testing was used more than blood-borne infections (HIV and hepatitis) testing. It may have been more convenient (a sampling kit could be ordered and returned by post and there was no need to visit a laboratory in person), and more attractive as there have been several HIV testing campaigns for MSM in Estonia, but there are no free-of-charge and anonymous STI testing opportunities [5]. The participants concerned about confidentiality may have considered it also more anonymous.

Testing during the study period was independently associated with Russian as the first language, living in towns/cities and having ever been tested for HIV. No other sociodemographic and behavioural indicators (including recent sexual risk behaviours) were related to testing. Men who had ever been tested for HIV were more likely to test during this study. This may indicate a habit for testing or personal attitudes and values which support testing and/or participation in research projects. Our dependent variable was 'testing during the study'. We did conduct separate analysis for those who were tested only for STIs or for blood-borne infections and also for those who were tested for both, but no other associations were found. One reason could be the very small sample size.

Despite the Internet-based questionnaire and testing sites in six larger cities in Estonia, the vast majority of participants were still from larger cities: the capital city, Tallinn, and surrounding Harju county (population 430,000) and the second largest city, Tartu (population size 99,500), as in previous studies [8–11]. Also, most of the MSM tested were from Tallinn (n=57; 84%), eight men were from Tartu and three from other regions. It may be related to the fear of being identified as gay or testing for STIs in general in smaller communities. The proportion of gay people in smaller communities may be very low, as many gay people may choose to move to the capital city, where they can be more anonymous and also experience less stigma.

The sample size for testing (n=68) was comparable with the previous studies [7,18]. As time and resources are at a premium in case of limited resources for active surveillance, we consider that one of the advantages of our approach lay in using the existing laboratory network. Thus we avoided the costs related to setting up special study sites and engaging personnel (as was the case with RDS and venue-based studies). The self-collection of urine samples worked well: all samples sent to the laboratory were suitable for processing. We received no complaints from the participants. The vast majority (91%) were tested within one month of answering the questionnaire.

We detected one case each of gonorrhoea and chlamydia (not LGV). No LGV cases have yet been reported in Estonia [3]. The limitation of our project was STI testing only from urine samples, so possible rectal and pharyngeal STI cases were missed.

HAV antibody prevalence among non-vaccinated men was 32%. This prevalence rate is in accordance with the previous studies. According to Tefanova and colleagues [23], the prevalence of hepatitis A among 20–29 year olds in Estonia was 41%. According to the World Health Organization, the proportion of people in eastern Europe who are immune to hepatitis A by the age of 40 years is 75% [24].

Self-reported HIV prevalence was 4%, and 7% of the men who were tested for HIV during the study were found to be positive. Both rates are somewhat higher than in previous studies [6,18]. Unfortunately, our sample size was too small for us to make definite conclusions about HIV trends among MSM in Estonia. However, the data on self-reported sexual behaviours show that many participants take risks, and so there is a possibility for further spread of HIV and other STIs among MSM.

MSM are not a priority group for HIV prevention in Estonia. The Internet, which provides a useful venue for delivering HIV/STI prevention and safer sex messages to MSM, could be better used, especially since gay-oriented bars, clubs and saunas (where condoms and lubricants are provided for free) only reach MSM in Tallinn and those MSM who are most likely to be open about being gay [5]. Considering that there are no gay-friendly sexual health services in Estonia, the system we have developed may be exploited in the future as an alternative venue for anonymous and free-of-charge STI and blood-borne infection testing among MSM. It could be further expanded by including sample kits for rectal and pharyngeal swabs, and also HIV home-test kits (currently not available in Estonia).

Limitations

One limitation of this study is that it was cross-sectional and we used a non-random sample. People who may have been more likely to participate include those with better-than-average access to the Internet, those who were more comfortable with technology, and those who were interested in free testing. The data were self-reported, and social desirability as well as recall bias may have been involved. In order to secure the anonymity of our participants we did not collect IP addresses, and so it was possible for one person to submit two or more questionnaires.

Conclusions

Linking Internet-based behavioural data collection with biological sample collection is a promising approach for studying hard-to-reach populations and merits further development. Further research is needed to determine the characteristics of people who opt to test in such studies and thereby the representativeness of the prevalence data. Considering the high prevalence of risk behaviours and low testing rates, higher priority to MSM sexual health should be given when planning HIV/STI prevention strategies.

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Conflict of interest

None declared.

Authors' contributions

KR, LL and JJ designed the study. KR supervised the data collection. KR and LL designed the data analysis and LL conducted the statistical analysis. KR wrote the first draft of the manuscript. All of the authors contributed to the final version of the manuscript. All of the authors read and approved the final manuscript.

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Anal human papillomavirus and HIV: A cross-sectional study among men who have sex with men in Moscow, Russia, 2012–2013

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Anal human papillomavirus (HPV) is prevalent among men who have sex with men (MSM), but has not been studied in the Russian Federation. A cross-sectional survey and HPV genotyping were conducted among HIV seropositive (n=58) and seronegative MSM (n=65) in Moscow. Multivariable logistic regression was performed to identify correlates of infection with oncogenic HPV genotypes 16 and/or 18 (HPV 16/18). Forty per cent (49/124) of all MSM were infected with at least one anal HPV genotype, 31.5% (39/124) had HPV16/18, and 11.5% (14/121) had high-grade squamous intraepithelial lesions (HSIL). HPV 16/18 was more prevalent in HIV seropositive than seronegative men (24/58, 41.4% vs 15/65, 23.1%; p=0.03). HIV infection was independently associated with HPV 16/18 (adjusted odds ratio (AOR): 5.08; 95% confidence intervals (CI): 1.49–17.34, p=0.01), as was having 2–4 steady male sex partners in the last year (vs ≤ 1 partner; AOR: 6.99; 95%CI: 1.94–25.24, p<0.01). History of prison/detention, migration to/within Russia and use of incompatible lubricants were marginally associated with HPV 16/18 (p<0.10). Comprehensive prevention options are needed to address HIV and HPV infection among MSM in Russia and may benefit from inclusion of young men in piloted HPV vaccination programmes.

Introduction

Globally, men who have sex with men (MSM) have the highest prevalence of human papillomavirus (HPV), high-grade anal dysplasia (pre-cancer) and anal squamous cell cancer (ASSC), compared with other risk groups [1]. The presence of high-risk (HR) HPV (types 16 and 18) in particular is closely associated with the progression from low-grade squamous intraepithelial lesions (LSIL) to high-grade SIL (HSIL) and also with ASSC [2–4]. This prevalence and incidence is more common in MSM infected with HIV [2,5]. In particular, there is an increased prevalence of HPV infections among MSM living with HIV, with a 35.4% pooled HPV 16 prevalence and anal cancer incidence of 45.9 per 100,000 HIV-infected men, as estimated by a recent meta-analysis [4]. Comparatively, in that same meta-analysis, HPV 16 prevalence was estimated to be 12.5% in HIV-uninfected men, with an anal cancer incidence of 5.1 per 100,000 men [4]. Evidence also suggests increased risk for HIV acquisition during infection with oncogenic HPV and persistent HPV infection is more common among men living with HIV compared with uninfected men [6].

Most epidemiological data on HPV in MSM is from North America, western Europe, and Oceania [4]. While recent epidemiological investigations have demonstrated high-risk sexual behaviours and up to 15% HIV prevalence among Moscow-based MSM, substantially higher than the 1% prevalence in the general adult population, HPV infection has not been a focus of research or public health surveillance among MSM in the Russian Federation [7–11]. Currently, estimates of the proportion of anal cancers that may be attributable to HPV in eastern Europe and central Asia are currently unavailable. Other modelling estimates from the Statistical Office of the European Union (Eurostat), however, suggest that of 72,694 new cancer cases each year among European men, 17,403 of these could be attributable to HPV and 15,497 attributable to high-risk HPV genotypes [12]. Approximately 30% of all new annual European cancer cases attributable to HPV16/18 are estimated to occur in men [12].

In light of the lack of information on anal HPV infection among MSM and potential co-infection among those living with HIV in the Russian Federation, this study aimed to explore the existence of anal HPV infection among HIV seronegative and seropositive MSM as well as correlates of infection with oncogenic HPV genotypes 16 and/or 18. Nested within a large epidemiological study of HIV among MSM in Moscow, circulating anal HPV genotypes, anal dysplasia, and other sexually transmitted infections (STIs) among HIV seropositive and seronegative MSM were evaluated.

Methods

Study population and site

Between January 2012 and January 2013, HIV seropositive and seronegative men (n=124) were enrolled from a pool of participants enrolled in a larger cross-sectional study of homosexual, bisexual and other MSM based in Moscow. This parent study also sought to compare the efficiencies of respondent-driven sampling (RDS) and Internet-based sampling (IBS) methods for recruiting MSM for HIV testing and counselling. Eligibility criteria for the parent study included adult men (age › 18 years) who reported anal sex with another man in the last 12 months.

Parent study participants were sampled via RDS and IBS, surveyed, and completed rapid HIV and syphilis testing. Briefly, RDS is a chain recruitment method often used to achieve representative samples of hard-to-reach populations [13]. Recruitment began with three purposively-selected 'seeds' who were each provided with four study-specific coupons with which to recruit peer MSM from their social network into the study. Seeds were recruited from the pool of MSM who were involved in local HIV prevention programmes or had participated in prior formative research and were selected to represent a range of individual characteristics. Individuals who were recruited by seeds were assessed for eligibility, consented, and enrolled in the study. At completion of study activities, participants were then provided with three study coupons for further recruitment of peers, constituting a new wave of recruitment. This process continued and 31 waves of participants were ultimately enrolled. A full description of traditional RDS methodology can be found elsewhere [14]. RDS was conducted in Moscow between October 2010 and April 2013 while IBS recruitment took place from late October 2010 to November 2012. IBS recruitment was conducted through banner ads posted on dating websites for MSM, including *Qguys*, *Parniplus*, and *Bluesystems.ru*. When clicked, banner ads linked interested viewers to an online consent form and a brief 10-item online quiz to obtain information on sociodemographic characteristics, sexual identity, and sexual practices. No personal identifiers or IP addresses were obtained from participants. Participants who were preliminarily deemed eligible for the full study, based on online quiz responses, were then directed to a study information page. Participants from both IBS and RDS were provided with the study telephone number via webpage or coupon, respectively, and advised to call to schedule an appointment. All procedures from the appointment onward were the same for RDS and IBS participants.

Participants who completed parent study activities, which included an interviewer-administered survey and HIV and syphilis rapid and confirmatory testing, were assessed for eligibility to participate in a nested HPV sub-study. Because the of the small sample size and the primary interest of identifying circulating HPV genotypes, eligibility for the sub-study was limited to those who self-reported inconsistent condom use during receptive anal sex (last 12 months) to ensure that men who are at risk of HPV infection were included in the sub-study. The HPV sub-study targeted enrolment to relatively equal samples of participants by HIV serostatus. Research activities were conducted in a private health clinic that is known to be accepting of MSM and activities were implemented by a local non-governmental organisation, AIDS Infoshare, which has a history of HIV research with key populations. All activities were conducted in the Russian language and all data collection and testing was anonymous. Remuneration for participation in the sub-study was RUB 2,000 (approximately EUR 50).

Survey measures

As part of the parent study, all participants were asked to complete an anonymous, interviewer-administered, structured survey to capture information on demographics, history of HIV and STI prevention and service use; sexual behaviours with men and women, including anal/oral/vaginal sex; number of sexual partners and partner characteristics; transactional sex (purchased or sold); and substance use. Sexual behaviour measures were adapted from the United States Centers for Disease Control and Prevention (CDC)'s National Health Behavior Survey [15]. Participants who reported past diagnosis of HIV infection were asked additional questions about HIV care and treatment. Additional sexual behaviour questions were asked of HPV sub-study participants to determine if any items had been placed in the anal canal within the last 24 hours, such as douching, use of sex toys, and anal sex, that might impair tests or result in indeterminate results. Computer-based surveys were administered by trained AIDS Infoshare interviewers and time for survey completion ranged from 60 to 90 minutes.

Biological sampling and testing

MSM were tested for HIV and syphilis infection within the parent study; these procedures have been described elsewhere [7]. Briefly, syphilis infection was measured with Lues rapid plasma reaction (RPR) (Nearmedic Plus, Moscow, Russia) and those samples testing positive for syphilis were confirmed with Lues RPGA test (Nearmedic Plus, Moscow, Russia). HIV testing used Determine HIV-1/2 test (Abbott Laboratories, Abbott Park, IL, US) rapid tests. Samples from those

Table 1

Demographic characteristics of Moscow-based men who have sex with men, stratified by HIV serostatus, cross-sectional study, Moscow, Russia, January 2012–January 2013 (n=123)

	HIV seronegative (n=65)		HIV seropositive (n=58)		p value	Total	
	n	Col %	n	Col %		n	Col %
Age (years)					0.03		
‹25	24	36.9	10	17.2		34	27.6
25 to 29	20	30.8	17	29.3		37	30.1
30 to 35	10	15.4	20	34.5		30	24.4
›35	11	16.9	11	19.0		22	17.9
Place of birth					0.60		
Russia	56	86.2	48	82.8		104	84.6
Outside Russia	9	13.8	10	17.2		19	15.4
Moved to or within Russian Federation for work (n=122)					0.42		
No	41	64.1	33	56.9		74	60.7
Yes	23	35.9	25	43.1		48	39.3
Sexual identity					0.65		
Homosexual	44	67.7	37	63.8		81	65.9
Bisexual	21	32.3	21	36.2		42	34.1
Ever married to a woman					0.29		
Never	59	90.8	49	84.5		108	87.8
Past/current marriage	6	9.2	9	15.5		15	12.2
Number of dependents					0.17		
1	43	66.2	38	65.5		81	65.9
2 to 3	22	33.8	17	29.3		39	31.7
≥4	0	0.0	3	5.2		3	2.4
Education (level completed)					0.99		
Primary education	1	1.5	1	1.7		2	1.6
Secondary education	17	26.2	13	22.4		30	24.4
Specialised secondary education (diploma)	21	32.3	18	31.0		39	31.7
Undergraduate education	6	9.2	6	10.3		12	9.8
Higher education	20	30.8	20	34.5		40	32.5
Employment categories (n=121)					0.50		
Full-time	31	49.2	26	44.8		57	47.1
Part-time	26	41.3	22	37.9		48	39.7
Student only	3	4.8	2	3.4		5	4.1
Other, including retired, disabled	0	0.0	1	1.7		1	0.8
Unemployed	3	4.8	7	12.1		10	8.3
Income level					0.22		
Poverty	2	3.1	5	8.6		7	5.7
Low	37	56.9	25	43.1		62	50.4
Middle	25	38.5	28	48.3		53	43.1
High	1	1.5	0	0.0		1	0.8
Usual healthcare provider (n=117)					0.73		
Private only	18	29.0	12	21.8		30	25.6
Public and private/other	11	17.7	9	16.4		20	17.1
Public only	32	51.6	32	58.2		64	54.7
Other only	1	1.6	2	3.6		3	2.6

Col: column.

Table 2

HPV and anal cytology results among MSM in Moscow, Russia, stratified by HIV serostatus (n=123)

	HIV seronegative (n=65)		HIV seropositive (n=58)		p value	Total	
	n	Col %	n	Col %		n	Col %
Anal cytology results (n=120)					0.81		
Normal	57	87.7	49	89.1		106	88.3
HSIL	8	12.3	6	10.9		14	11.7
Infection with HPV genotype							
6[a] (ref: no)	7	10.8	13	22.4	0.08	20	16.3
11 (ref: no)	4	6.2	4	6.9	0.87	8	6.5
16 (ref: no)	9	13.8	11	19.0	0.44	20	16.3
18[b] (ref: no)	4	6.2	12	20.7	0.02	16	13.0
31 (ref: no)	8	12.3	9	15.5	0.61	17	13.8
33 (ref: no)	7	10.8	5	8.6	0.69	12	9.8
Any HPV genotype[b] (ref: no)	20	30.3	29	50.9	0.04	49	39.8
HPV16/18a (ref: no)	15	23.1	24	41.4	0.03	39	31.7

Col: column; HSIL: high-grade squamous intraepithelial lesions; HPV: human papilloma virus; Ref: reference category not displayed

[a] p-value<0.10;
[b] p-value<0.05

testing positive were sent to the local reference laboratory for confirmatory testing. The clinic staff physician provided pre- and post-test HIV counselling and followed all federal protocols [16]. For the purposes of the HPV study, participants are defined as HIV seropositive or seronegative, based on confirmatory study results.

Participants of the HPV sub-study provided additional biological specimens for testing for urethral, oral, and rectal gonorrhoea and chlamydia, as well as for anal cytology and anal HPV genotyping. All specimens for the sub-study were collected by the same study physician and transferred daily for laboratory analysis by a local reference laboratory (Lages Laboratory, Moscow, Russia).

Anorectal specimens were first collected for anal cytology (Papanicolaou (Pap) test) to detect HPV-associated anal dysplasia and followed by anorectal specimen collection for HPV genotyping. Both specimens were collected by inserting a saline-moistened polyester swab into the anal canal into the rectum to ensure sampling of the anorectal transition zone. The swab was rotated slowly during withdraw to capture cells. HPV testing of swabbed cellular material was conducted at the reference laboratory using PCR for amplification of a fragment of the L1 gene to detect the following HPV genotypes: 6, 11, 16, 18, 31, and 33.

Rectal specimens to test for gonococcal and chlamydial infection were then collected by polyester swab inserted at least 2 inches beyond the anal margin and withdrawn in a rotating motion. Participants had the option to provide urethral swabs or urine specimen collection to test for urethral gonococcal and chlamydial infection. The local reference laboratory analysed swabs and urine specimens for gonococcal and chlamydial infection using nucleic acid amplification tests (DiaGen, Moscow, Russia).

All tests, except those for HPV, were performed within 2–3 days of collection, so that participants could be informed of their test results and provided with treatment according to national treatment standards for genital warts, gonorrhoea, syphilis, and chlamydia. Treatment was provided by the study clinic. Participants who screened positive for anal dysplasia by cytology were provided with referrals to the Institute of Proctology in Moscow, where the participant could receive specialised care. Participants with HPV infection, with exception of those with HPV-related genital warts, were not informed of HPV test results as testing was conducted in batches and no treatment was available for men.

Statistical analysis

Descriptive analyses were conducted to estimate the distribution of HPV genotypes, STIs, behavioural characteristics, sexual health history, and use of antiretroviral therapy (ART). Bivariate analysis was used to compare distributions of HPV genotypes among participants with and without HIV infection as well as to compare distributions of characteristics of participants with and without HPV 16/18 infection. HPV 16 and 18 were the focus of this analysis due to the attribution of HPV 16 or 18 to most anal cancers and the inclusion of these genotypes in the quadrivalent vaccine. Chi-squared tests were used to evaluate statistical significance in bivariate analysis. HIV status, known confounders (such as age), and variables that test at least

Table 3A

Distribution of demographic and sexual behaviour characteristics among men who have sex with men in Moscow, Russia, by oncogenic human papilloma virus infection (n=124)

	No HPV 16/18 infection (n=95)		HPV 16/18 infection (n=29)		p value	Total	
	n	Col %	n	Col %		n	Col %
Demographics					0.81		
Age, years					0.14		
‹25	30	31.6	4	13.8		34	27.4
25–29	25	26.3	12	41.4		37	29.8
30–35	21	22.1	9	31.0		30	24.2
›35	19	20.0	4	13.8		23	18.5
Born in Russia (ref: born outside of Russia)	82	86.3	23	79.3	0.36	105	84.7
Homosexual identity (ref: bisexual)	61	64.2	21	72.4	0.41	82	66.1
Ever married to a woman (ref: never)	12	12.6	3	10.3	0.74	15	12.1
Moved to or within Russian Federation for work (n=123; ref: no)[a]	32	33.7	16	57.1	0.03	48	39.0
Usual healthcare provider (n=118)[b]					0.07		
Private only	24	26.7	6	21.4		30	25.4
Public and private/other	12	13.3	8	28.6		20	16.9
Public only	53	58.9	12	42.9		65	55.1
Other only	1	1.1	2	7.1		3	2.5
Lifetime history of prison/detention (ref: no)[a]	5	5.3	7	24.1	0.01	12	9.8
Sexual behaviours							
Ever disclosed sexual identity/ behaviour to others (n=121; ref: no)	70	75.3	25	89.3	0.11	95	78.5
Age of first sex (n=122)					0.73		
‹=18	61	64.9	16	57.1		77	63.1
19–25	31	33.0	11	39.3		42	34.4
›25 yrs.	2	2.1	1	3.6		3	2.5
No. of male sexual partners (last 12 months)					0.58		
One or less	16	16.8	4	13.8		20	16.1
2 to 4	20	21.1	4	13.8		24	19.4
5 or more	59	62.1	21	72.4		80	64.5
No. of steady male partners (last 12 months) [a,c]					0.02		
One or less	60	64.5	13	48.1		73	60.8
2 to 4	20	21.5	13	48.1		33	27.5
5 or more	13	14.0	1	3.7		14	11.7
Received money/goods for sex (last 12 months; n=118; ref: no)	36	39.1	8	30.8	0.44	44	37.3
Paid money/goods for sex (last 12 months; n=118; ref: no)[a]	24	26.7	2	7.1	0.03	26	22.0
Use alcohol or drugs before sex (last 12 months; n=120)					0.27		
Alcohol only	59	63.4	18	66.7		77	64.2
Drugs only (including poppers)	1	1.1	2	7.4		3	2.5
Both alcohol and drugs (including poppers)	19	20.4	4	14.8		23	19.2
Neither	14	15.1	3	11.1		17	14.2
Incompatible lubricant used during sex (n=121; ref: Compatible)[b]	36	38.7	16	57.1	0.08	52	43.0

ART: antiretroviral therapy; *C. trachomatis*: *Chlamydia trachomatis*; Col: column; HPV: human papilloma virus; HSIL: high-grade squamous intraepithelial lesions; *N. gonorrhoeae*: *Neisseria gonorrhoeae*; Ref: reference category not displayed.

[a] p-value‹0.05

[b] p-value‹0.10

[c] Steady partner was defined as 'another man whom you consider to be your boyfriend or partner and to whom you are most committed.'

Table 3B

Distribution of demographic and sexual behaviour characteristics among men who have sex with men in Moscow, Russia, by oncogenic human papilloma virus infection (n=124)

	No HPV 16/18 infection (n=95)		HPV 16/18 infection (n=29)		p value	Total	
	n	Col %	n	Col %		n	Col %
Sexually transmitted infections, HIV serostatus and treatment							
HSIL (n=121; ref: normal)[a]	7	7.6	7	24.1	0.02	14	11.6
Positive rectal *N. gonorrhoeae* results (n=124; ref: negative)	4	4.2	3	10.3	0.21	7	5.6
Positive urine/urethral *N. gonorrhoeae* results (n=123; ref: Negative)	1	1.1	0	0.0	0.58	1	0.8
Positive rectal *C. trachomatis* results[a] (n=124; ref: negative)	6	6.3	6	20.7	0.02	12	9.7
Positive urine/urethral *C. trachomatis* results (n=122; ref: Negative)	5	5.3	2	7.1	0.72	7	5.7
Positive syphilis results (n=123; ref: negative)	13	13.7	7	24.1	0.36	20	16.1
HIV seropositive (n=123; ref: negative)[a]	39	41.5	19	65.5	0.02	58	47.2
Last CD4 count (among 7 HIV seropositive men who had ever had a CD4 test)					0.65		
>500 cells/µL	1	25.0	1	33.3		2	28.6
200 –500 cells/µL	2	50.0	2	66.7		4	57.1
<200 cells/µL	1	25.0	0	0.0		1	14.3
Currently on ART (n=11; ref: no)	2	33.3	2	40.0	0.82	4	36.4

ART: antiretroviral therapy; *C. trachomatis*: *Chlamydia trachomatis*; Col: column; HPV: human papilloma virus; HSIL: high-grade squamous intraepithelial lesions; *N. gonorrhoeae*: *Neisseria gonorrhoeae*; Ref: reference category not displayed.

[a] p-value<0.05

[b] p-value<0.10

[c] Steady partner was defined as 'another man whom you consider to be your boyfriend or partner and to whom you are most committed.'

marginally significant in bivariate analysis (p<0.10) were used to construct a multivariable logistic regression model to identify independent factors associated with infection with HPV 16/18. Statistical significance was set at p<0.05 and marginal significance at p<0.10. Sensitivity analyses were conducted to evaluate the associations with HPV 16/18 when the comparison group comprised only those with no HPV infection of any kind. Data were not weighted for RDS network size during modelling, given that participants of this sub-study were selected on the basis of HIV status and using both RDS and IBS sampling methods. All statistical analyses were conducted using Stata version 12 (StataCorp, College Station, TX, USA).

Research ethics

The study was conducted in partnership with a local non-governmental organisation, AIDS Infoshare, and approved by both the Ethics Committee of the State Medical University, IP Pavlov, Saint Petersburg, Russia and the Johns Hopkins Bloomberg School of Public Health Institutional Review Board, Baltimore, Maryland, USA.

Results

Final enrolment of HPV sub-study participants included 124 MSM, of whom 58 were HIV-seropositive, and 65 HIV seronegative, based on confirmatory testing, and one with indeterminate HIV test results. Four participants who reported a past diagnosis of HIV, tested positive by rapid test, and declined further confirmatory testing were included among the sample of HIV-seropositive participants. One participant provided only a rapid test, which was negative, but had reported a past diagnosis of HIV infection. This participant's HPV and behavioural data were included in the analysis, but HIV status was considered indeterminate for this analysis. No indeterminate HPV results were returned for any of the 124 sub-study participants. Three participants had indeterminate anal cytology results, yielding a final anal cytology sample of 121.

Table 1 presents demographics and select sexual practices of participants in the sub-study, stratified by HIV serostatus. Overall, participants had a median age of 29 years (range: 19–50 years) though HIV-seropositive participants tended to be slightly older, compared with seronegative participants (p=0.03). No other differences across HIV serostatus existed among collected demographic characteristics.

All evaluated HPV types were present among study participants and 39.5% (49/124) were diagnosed with infection by at least one HPV genotype. Table 2 presents HPV diagnoses among MSM participants, stratified by HIV serostatus. Infection with any HPV genotype was higher among HIV seropositive men (29/58; 50.0%) compared with seronegative men (20/66, 30.3%; p=0.04). Some 41.4% (24/58) of seropositive men were identified with HPV 16/18 compared with 23.1% among seronegative men (15/65; p=0.03).

Table 4*

Crude and adjusted associations of demographic and sexual behaviour characteristics with human papilloma virus 16/18 infection among men who have sex with men in Moscow, Russia (n=124)

	Crude analysis				Adjusted analysis[a]			
	OR	95% CI		p value	AOR	95% CI		p value
Demographics								
Moved to or within Russian Federation for work (n=123)[b,c]								
No	Ref				Ref			
Yes	2.63	1.11	6.21	0.03	3.18	1.00	10.09	0.05
Usual healthcare provider (n=118)[d]								
Private only	Ref							
Public and private/other	2.67	0.75	9.45	0.13				
Public only	0.91	0.30	2.70	0.86				
Other only	8.00	0.62	103.67	0.11				
History of prison/detention[b,e]								
No	Ref				Ref			
Yes	5.66	1.64	19.55	0.01	6.53	0.85	50.42	0.07
Sexual behaviours								
No. of steady male partners (last 12 months) [b,c,f]								
One or less	Ref				Ref			
2 to 4	3.00	1.20	7.53	0.02	6.99	1.94	25.24	P<0.01
5 or more	0.36	0.04	2.96	0.34	0.14	0.01	2.09	0.16
Purchased sex (last 12 months; n=118)[b,e]								
No	Ref				Ref			
Yes	0.21	0.05	0.96	0.04	0.23	0.04	1.26	0.09
Type of lubricant used during sex (n=121)[d,e]								
Condom compatible	Ref				Ref			
Incompatible	2.11	0.90	4.97	0.09	2.84	0.86	9.44	0.09
Sexually transmitted infections								
Rectal *C. trachomatis* results[b]								
Negative	Ref				Ref			
Positive	3.87	1.14	13.12	0.03	3.17	0.67	14.90	0.15
HIV diagnosis (n=123)[b,c]								
Seronegative	Ref				Ref			
Seropositive	2.68	1.12	6.39	0.03	5.08	1.49	17.34	0.01

AOR: adjusted odds ratio; *C. trachomatis: Chlamydia trachomatis*; CI: confidence intervals; OR: odds ratio.

[a] The final model included HIV status, rectal Chlamydia infection, migration to/within Russia, lifetime history of detention in prison, number of steady male sex partners, type of lubricant typically used during anal sex with men (condom compatible v. incompatible), and age (continuous); Dependent variable reference group is no HPV 16/18 infection;

[b] Crude analysis p-value for total variable<0.05;

[c] Adjusted analysis p-value for total variable<0.05;

[d] Crude analysis p-value for total variable <0.10;

[e] Adjusted analysis p-value for total variable <0.10;

[f] Steady partner was defined as 'another man whom you consider to be your boyfriend or partner, to whom you are most committed.'

HPV genotypes among HIV seropositive MSM demonstrated slightly different patterns and prevalence compared with HIV seronegative men. Among the total sample, prevalence of HSIL was 11.7%, with no difference by HIV serostatus (p=0.81).

Table 3 presents the distribution of sexual and health behaviours among participants with and without HPV 16/18 infection. Participants were similar across most demographic characteristics. Among those with HPV 16/18, over 57.1% (16/28) had moved within or into Russia for work, compared with 33.7% of those without HPV 16/18 (32/95; p=0.05). Likewise, 24.1% (7/29) of those with HPV 16/18 infection had a lifetime history of detention or prison, compared with 5.3% of those without HPV 16/18 (5/94; p=0.01). Differences were observed across some sexual behaviours. Higher proportions of MSM with HPV 16/18 tended to report greater numbers of steady male sexual partners than those without HPV 16/18 infection (p=0.02), although the total numbers of male sexual partners in the last 12 months did not differ by HPV infection. Over half of

MSM with HPV 16/18 infection (57.1%; 16/28) reported the use of a condom-incompatible lubricant or no lubricant (incompatible lubricants are those which are not water- or silicon-based, including oils and lotions), which was marginally higher than those without infection (36/93; 38.7%; p=0.08). HSIL (p=0.02) and rectal infection with Chlamydia trachomatis (p=0.02) were associated with HPV 16/18 infection HSIL was present among 24.1% (7/29) of participants with HPV 16/18 infection, compared with 7.6% of those without HPV16/18 (7/92; p=0.02). In the sensitivity analysis (data not shown) with a comparison group of those without any HPV infection, patterns of association were similar to those in Table 3.

Table 4 presents crude and adjusted associations with HPV 16/18 infection. HIV infection was independently associated with HPV 16/18 infection (adjusted odds ratio (AOR): 5.08; 95% confidence intervals (CI): 1.49–17.34; p=0.01), as was having 2–4 steady male sex partners in the last year (vs ≤ 1; AOR: 6.99; 95% CI: 1.94–25.24; p<0.01). History of prison or detention (AOR: 6.53; 95% CI: 0.85–50.42; p=0.07), use of incompatible lubricants (AOR: 2.84; 95% CI: 0.86–9.44; p=0.07), and migration to/within Russia (AOR: 3.18; 95% CI: 1.00–10.09; p=0.05) were marginally associated with HPV 16/18. Rectal infection with C. trachomatis was no longer associated with HPV 16/18 after adjustment for other variables, though the magnitude of the odds ratio suggests potential association. In the sensitivity analysis (data not shown) for the crude and adjusted logistic regression, HIV infection, rectal C. trachomatis infection, history of moving to/within the Russian Federation, having 2–4 steady male partners were independently associated with HPV16/18.

Discussion

HPV, particularly its oncogenic genotypes, is prevalent among this sample of Moscow-based MSM and more common among those living with HIV infection. All tested genotypes were detected among the total sample, with 41.2% infected with at least one HPV genotype, the majority of which were comprised of HPV 16 or 18 genotypes. To a lesser degree, HSIL was also identified among this sample. HPV 16/18 infection was significantly or marginally associated with structural factors, sexual behaviours, and individual biological factors. In this context, HIV infection may act as a biological factor for HPV infection, as well as serving as a marker for sexual risk. While rectal C. trachomatis infection was not significant after inclusion in the full model, the magnitude of the odds ratios suggests that such infections may be related to HPV 16/18, which is consistent with studies in other settings [17]. These data represent the first data on HPV and anal dysplasia in MSM from the Russian Federation, as well as the wider EECA Region.

Consistent with other research of HPV in MSM, HPV 16/18 was associated with individual sexual behaviours [3,18]. In this study, HPV was specifically associated with higher numbers of steady male sexual partners in the last 12 months. While there was no difference across the total numbers of sex partners within the last 12 months, the association with the number of steady partners may actually reflect the sexual relationships where condoms are most inconsistently used, given that condoms tend to be used more consistently during relationships with new partners [9,19]. Additionally, increased numbers of steady partners among MSM with HPV 16/18 infection may reflect more transient relationships and greater risk behaviour among this subgroup. HPV 16/18 was also associated with regular use of lubricants that are incompatible with latex condoms. Oil-based lubricants or other methods of lubrication (such as body lotion) have been shown to degrade latex condoms during use, potentially facilitating exposure to HPV infection during anal intercourse [20]. Simple interventions that improve condom use with all sexual partners and increase use of condom-compatible lubricants may reduce HPV transmission, as well as HIV and other STIs.

Several structural factors were marginally associated with HPV 16/18. These factors included history of detention in prison and migration to or within the Russian Federation. These may be markers of exposures to new networks in which HPV and/or HIV may be prevalent (e.g. among MSM networks in prison or in a new city) or may reflect low access to prevention methods for HIV/STI [9,21]. In the absence of data on HPV in Russia or EECA, understanding of HPV transmission related to these structural factors may be derived from research on HIV and other STI. An Internet survey conducted among MSM in 38 European countries in 2010 found that around 65% of Russian men had received information about how STIs can be transmitted during same-sex practices and only 50% had accessed HIV prevention programmes. These indicators for information and access to HIV prevention were below the median estimates for their European counterparts [22]. For those detained in prison/detention or who are new migrants, access to information and prevention methods may be even more limited [23]. Condoms and other HIV prevention methods are not available within prisons or detention facilities in Russia, despite evidence of exposure opportunities and transmission within prisons in Russia and wider EECA countries [24,25]. During detention, HIV, HPV and other STI transmission may occur through consensual same sex behaviours, rape or other non-consensual practices, and HIV exposure through shared syringes among those who inject drugs [24]. Outside of prison or detention, access to public healthcare is limited by the propiska-like system that requires individuals to be registered and hold documentation for their city of residence. For migrant populations, including internal migrants, this limits access basic HIV and STI prevention [23,26]. In other European countries, migration status has been associated with increased prevalence of HIV and STI infection [27].

Findings should be viewed in light of several limitations. First, this was a small, cross-sectional study to explore circulating HPV and oncogenic HPV genotypes among MSM in Moscow, Russia; thus, this small sample size limits statistical power and broader inferences. Selection on the basis of HIV status and self-reported inconsistent condom use may bias the estimates of HPV prevalence. Consistent with other socio-behavioural surveys, additional bias may be introduced with the length of the survey and/or selection bias associated with presenting to the study clinic for participation and participant incentives. As such, these data are not intended to provide prevalence estimates for the country or Moscow city, but provide insight into anal HPV infection among Moscow-based MSM and circulating genotypes. Findings from the multivariable analysis are informative for future research, but the generalisability may be limited by the small sample and non-random sampling method and should be interpreted with caution. Studies with larger samples and prospective analyses are needed to fully understand correlates or predictors of HPV infection among Russian MSM. Data were not collected on smoking duration or dose, which is a known risk factor for progression to HSIL and is relevant in Russia where smoking remains very common [3]. As this was a cross-sectional study, longitudinal data on anal clearance rate of the different HPV types or persistence of infection were not collected and further research is warranted, as persistence has been significantly greater for persons living with HIV, compared with those who are uninfected [6,18].

Interventions to reduce HPV transmission among MSM in the Russian Federation are warranted. Both the quadrivalent and bivalent vaccines have demonstrated efficacy against oncogenic HPV-vaccine-type infections in MSM and other men [28]. Modelling estimates have taken such findings further and estimated an 86% reduction in HPV 16/18-related carcinomas among men in Europe with implementation of vaccination of girls and boys vs screening alone [29]. Relative to a female-only programme, vaccination of both genders has demonstrated a greater reduction in male and female HPV-related carcinomas [29]. The quadrivalent HPV vaccine has been licensed for use in Russia and is being tested in school-based, pilot programmes for adolescent girls in four Russian cities, including Moscow, though regional experts have recommended inclusion of boys in vaccination campaigns [30,31]. While HIV prevention programmes for MSM in the Russian Federation are limited by stigmatization and laws ban 'homosexual propaganda', equitable HPV vaccination programmes for young men and women in the country may impart benefit without requiring disclosure of sexual preferences [32, 33]. Research from North American settings also support the use of anal Pap screening among MSM as an acceptable means of secondary prevention, though cost-effectiveness analyses have yielded mixed results [34,35].

Prevention of HPV infection among MSM in the Russian Federation - and ultimately prevention of HSIL - may rely on basic tenets of HIV prevention: condom distribution and ART treatment for those living with HIV. Enabling access to and encouraging use of appropriate condoms and compatible lubricants with all partners during anal intercourse provides protective barriers against HPV acquisition in the absence of other HPV prevention methods. Given that ART has also demonstrated protective benefits against oncogenic HPV, in addition to preventing onward transmission of HIV, HIV testing and access to ART care for MSM who are living with HIV remain critical [36,37]. As resources for HIV prevention among key populations in the Russian Federation become limited, programmes that are comprehensive and address multiple STIs, including HIV and HPV, and facilitate engagement with HIV care, may be most efficient and promising for protecting health of Russian MSM.

* Erratum:

The title of Table 4 was corrected on 28 April 2015.

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Conflict of interest

None declared.

Authors' contributions

CB, AW, CZ, NG, VM, AP, and CL collaborated in the design and oversight of the overall study. RC, IM, and AD provided additional expertise into the design and analysis of the HPV sub-study. IK and PD coordinated local study implementation and conducted data collection. AW wrote the initial drafts of this manuscript. AW conducted the statistical analysis and composed the initial draft of the paper. All authors had full access to the data, reviewed and edited the manuscript, and all take responsibility for its integrity as well as the accuracy of the analysis.

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A systematic review of evidence to inform HIV prevention interventions among men who have sex with men in Europe

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An estimated 42% of all newly diagnosed HIV cases in Europe in 2013 were transmitted during sex between men. This review was performed to identify and describe studies evaluating the efficacy and effectiveness of HIV prevention interventions among men who have sex with men (MSM), in relation to implementation data from European settings. A systematic search was performed individually for 24 interventions. Data were extracted from studies including efficacy or implementation data from European settings, appraised for efficacy, implementation and plausibility, and assigned a grade (1-4) according to the Highest Attainable Standard of Evidence (HASTE) framework. Four interventions (condom use, peer outreach, peer-led groups, and using universal coverage of antiretroviral treatment and treatment as prevention) were assigned the highest HASTE grade, 1. Another four interventions were assigned 2a for probable recommendation, including voluntary counselling and testing for HIV, using condom-compatible lubricant, using post-exposure prophylaxis, and individual counselling for MSM living with HIV. In addition, seven interventions were assigned a grade of 2b, for possible recommendation. Encouragingly, 15 interventions were graded to be strongly, probably or possibly recommended. In the relatively resource-rich European setting, there is an opportunity to provide global leadership with regard to the regional scale-up of comprehensive HIV prevention interventions for MSM.

Introduction

In 2012 the global burden of HIV was estimated to include 35.3 million people living with the virus (people living with HIV, PLWH). Among adults between the ages of 15–49 years old HIV prevalence was estimated at 0.8% [1]. Globally there is a declining trend in new infections, morbidity and mortality due to HIV/AIDS [2]. Improved treatment regimens and access to treatment are important factors behind these trends [2].

Gay, bisexual and other men who have sex with men (MSM) are disproportionately affected by HIV in every setting where data are available [3]. HIV rates reported among MSM show an increasing trend, in contrast to the declining trends reported in the general population [4]. A 2013 systematic review of HIV epidemiology in 33 high-income countries where data were available estimated a total of 2.3 million PLWH [5] and a male–female median case ratio of 2.5: 1 [5,6], indicating male-predominant epidemics. High-income countries where antiretroviral treatment (ART) and prevention services are available show increasing trends in HIV prevalence among MSM [5,7].

Of the 29,157 persons diagnosed with HIV and reported in the European Union/European Economic area (EU/EEA) in 2013, 42% of cases were estimated to be due to sex between men [8]. Since 2006, MSM represent the only key population where an increase in HIV diagnoses has been observed, with a 33% increase between 2004 and 2013 in the EU/EEA overall and with increases of more than 100% observed in some EU countries during the past decade, including Bulgaria, Cyprus, Czech Republic, Hungary, Romania, and Slovakia [9]. HIV prevalence among MSM was estimated to be at or above 5% in 14 of the 26 EU/EEA countries reporting national data in 2012 [10].

In accounting for the relatively higher rates of HIV among MSM compared with the general population, recent epidemic modelling highlights the importance of the higher transmissibility of HIV during unprotected anal intercourse (as opposed to vaginal) and the importance of insertive/receptive sexual role versatility among MSM [4,11]. Clusters of HIV transmission

indicative of outbreaks within sexual networks of MSM may also play an important role in the higher transmission probability reported [12-14].

The current picture of the HIV epidemic among MSM in Europe highlights significant variation between countries. Biological and behavioural surveillance systems vary across European countries, as do the extent of sexual health needs assessment, collaborative service planning and the availability of acceptable and accessible sexual health services [15]. Prevalence data for MSM, a population of unknown size, can be estimated in diverse ways and therefore prevalence rates may not be fully comparable between countries. Most European countries report the number of newly diagnosed cases annually [10].

Community, research, medical and public health efforts to prevent HIV have existed in Europe for over three decades, with European gay community organisations at the forefront of peer-led HIV prevention globally. However, overall national responses have been inadequate to contain HIV epidemics among MSM, with continuing high and in some countries increasing HIV incidence among MSM [5,16].

HIV prevention interventions for MSM are purposeful activities intended to increase the uptake of HIV precautionary behaviours or to reduce HIV risk behaviours. Intervention activities can target MSM directly, they can be directed to intermediaries who deliver activities to MSM, or they can influence the policy and service environment. The effectiveness of HIV prevention interventions among MSM has been assessed previously, most recently by the World Health Organization Global Guidelines process in 2010–11 [17]. In order to capture more recent data in the rapidly evolving field of HIV prevention and to ensure context-specific relevance, there was a need to update and extend the previous reviews and catalogue the evidence in order to inform MSM prevention interventions in Europe [18,19].

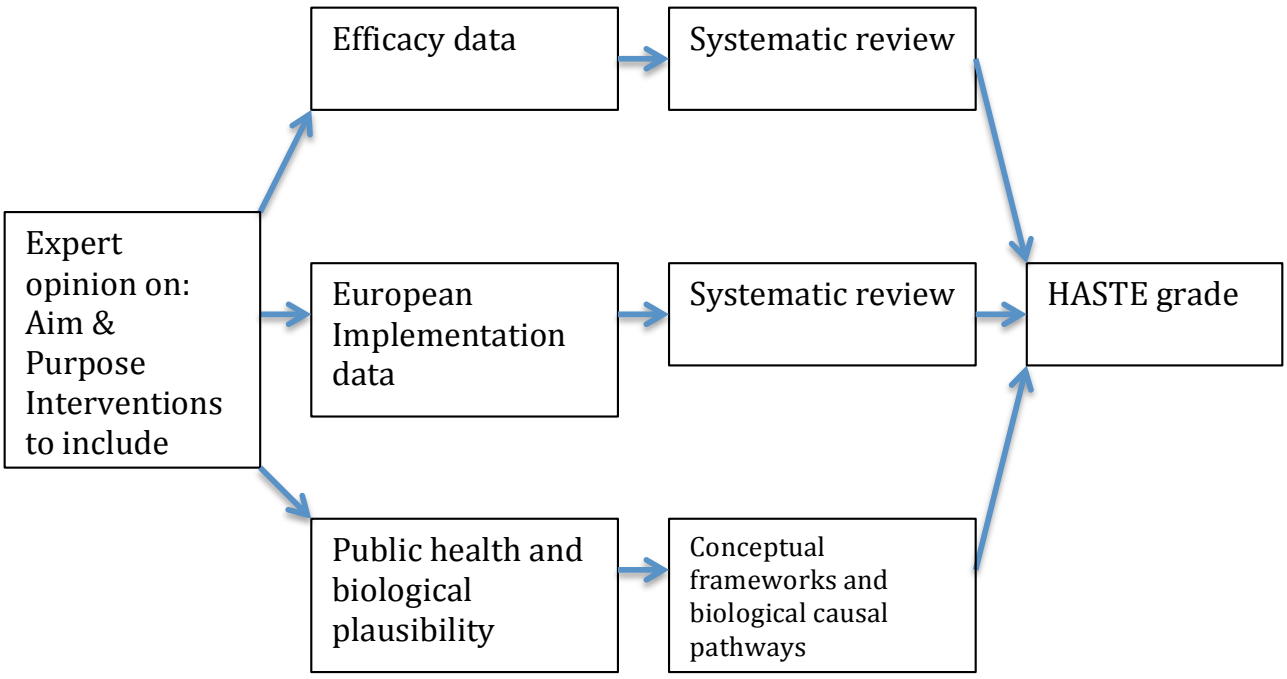
The objectives of this review were to identify and describe studies evaluating the efficacy, and effectiveness of HIV prevention interventions among MSM in relation to implementation data from the European setting, and to further appraise the evidence according to the Highest Attainable Standard of Evidence (HASTE) framework [20]. The review of evidence was performed in order to inform the development of guidance by the European Centre for Disease Control and Prevention (ECDC) to Member States on the commissioning and delivery of HIV prevention interventions to MSM in the EU/EEA [21].

Methods

In this review the term 'men who have sex with men' (MSM) refers to the population of men engaged in same-sex sexual behaviour, inclusive of sexual identities (e.g. gay, bisexual, straight, experimenting, etc.)

Figure

Work process for systematic review of HIV prevention interventions among men who have sex with men within the European setting, searches performed December 2012–February 2013



HASTE: Highest Attainable Standard of Evidence

Table 1

Highest Attainable Standard of Evidence (HASTE) system for HIV interventions[a]

Grade level		Strength of recommendation	Explanation
Grade 1		Strong	• High plausibility • Efficacy is consistent • Large body of consistent implementation data
Grade 2	Grade 2a	Conditional: probable	• Plausibility • Limited efficacy data • Consistently effective from implementation data
	Grade 2b	Conditional: possible	• Plausibility • Limited or inconsistent efficacy data • Limited or paucity of implementation data[b]
	Grade 2c	Conditional: pending	• Plausibility • Ongoing efficacy trials
Grade 3		Insufficient	• Undefined plausibility • Inconsistent data • Inconsistent or paucity of implementation data
Grade 4		Inappropriate	• Consistent data demonstrating lack of efficacy • Consensus from implementation data of inappropriate intervention

[a] Modified from [21]

[b] A modification has been made, adding paucity of implementation data to grade 2b.

and sexual desire. The term MSM includes people who identify as men, and therefore includes transgender men who have sex with men. Transgender women might share some biological risks with MSM such as receptive anal intercourse, but recent data shows a higher HIV burden in this group, indicating a different epidemic scenario [22], and therefore transgender women are not included as a sub-group of MSM in this review. We use the term MSM in this review recognising the diversity and heterogeneity of this group but also the limitations of this term.

First, we made a comprehensive list of known interventions that address primary HIV transmission among MSM, inclusive of biomedical, psychosocial, and programmatic interventions. The list was developed, discussed and agreed by an expert review group and included medical, social science and policy experts, programme implementers from non-governmental organisations and government representatives. The group was convened by the ECDC for the development of European guidelines on HIV prevention in MSM. A systematic review was performed for each intervention included (Figure 1).

Existing evidence from randomised controlled trials (RCTs) evaluating public health interventions with biological endpoints for MSM populations are limited, which highlights the need for strategies additional to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system when performing a review such as this [18,19,23]. The HASTE system builds on the GRADE system and was developed specifically to evaluate evidence regarding HIV/sexually transmitted infection (STI) interventions among most at-risk populations, in particular MSM [19]. HASTE takes into account three categories that are given equal weight: efficacy data, implementation science data and biological and public health plausibility (Table 1) [19]. Hill's criteria for causality remain the most relevant set of determinants of whether an intervention causes prevention and/or mitigation of disease in the HASTE grading system [24].

Implementation data were defined as data reporting on availability, acceptability, uptake, feasibility of implementation, implementation costs, and effectiveness of the intervention among MSM in the European setting.

Public health plausibility was defined as the intervention having a likely pathway leading to a decrease in HIV incidence. For example, HIV testing itself might not lead directly to lower HIV incidence, but it has a crucial role because it is on the pathway to uptake of ART for people living with HIV, which does decrease HIV onward transmission and HIV-related morbidity and mortality.

Search strategies

The Population, Intervention, Comparison, Outcome (PICO) model was used to develop inclusion criteria and search terms per intervention [25]. The population for the intervention was MSM. All types of comparison and no comparison were included. Outcomes included were biological markers (prevalence and incidence of HIV/STIs), self-reported diagnoses of HIV infection and self-reported behavioural outcomes on condom use or unprotected anal intercourse (UAI). Studies reporting on implementation data were only included if performed in Europe. Systematic reviews previously performed on these topics were included. Non-peer-reviewed literature was not used as a source of original

Table 2

Number of articles found through search strategies, screened and included according to inclusion criteria for HIV prevention interventions among men who have sex with men in Europe

Interventions	Articles identified through searches	Number of articles included addressing efficacy	Number of articles included addressing implementation
Condom use	130	1	3
Universal coverage of antiretroviral treatment and treatment as prevention	9	1	4
Peer-led group interventions	326	2	0
Peer outreach	326	2	0
Voluntary HIV counselling and testing	717	2	8
Condom-compatible lubricant use (when using condoms)	130	5	2
Post-exposure prophylaxis	28	3	2
Individual counselling for MSM living with HIV	327	4	2
Peer-led group interventions targeting MSM living with HIV	326	1	2
Sex venue-based interventions	25	1	8
Social marketing interventions	476	3	7
Individual counselling for MSM	327	2	1
Internet-based HIV prevention messages	40	6	4
Training for healthcare providers to provide comprehensive care for MSM	225	0	1
MSM friendly clinics	234	0	1
Voluntary anonymous partner notification	126	0	7
Voluntary medical male circumcision	49	3	2
Pre-exposure prophylaxis	4	1	0
Campaigns for lesbian, gay, bisexual and trans equality	3	0	1
Female condom use	4	3	1
Serosorting	9	3	4
Avoid ejaculation of semen orally	226	3	0
Avoiding poppers during anal intercourse	5	0	0
Reducing alcohol binge drinking among MSM	119	1	0
Total number of articles[a]	**3,865**	**47**	**60**

MSM: Men who have sex with men.

Searches were performed between 10 December 2012 and 8 February 2013.

[a] Search strategies captured the same articles to some extent.

data, but these documents did guide further searches for literature. Studies published in English, French, and Spanish were included. Studies not fitting these criteria were excluded from the review.

Electronic searches were performed in PubMed, Embase, Medline, Cinahl, PsycINFO, the Cochrane Library and the World Health Organization publication database. The search included medical subject headings (MeSH) terms for HIV or AIDS, and terms associated with MSM and the specific interventions reviewed (Annex I). Searches were particularly designed to be broad and comprehensive initially and were performed between 10 December 2012 and 8 February 2013. We reviewed the search strategies performed between 8 June 2010 and 17 March 2011 to guide the WHO's 2011 recommendations for 'Prevention and treatment of HIV and other sexually transmitted infections among MSM and transgender people', and where relevant these were updated up to 8 February 2013 [17].

Screening and data extraction

After the removal of duplicates, titles were screened independently by two researchers (SS, MS) to exclude those that did not fit the inclusion criteria. When a title was judged to be relevant, the abstract was reviewed and included if the inclusion criteria were met. When it was not clear whether the abstract met the inclusion criteria, the full article was reviewed.

For all selected articles, data were extracted by two researchers (SS, MS) using a pre-designed data extraction form that included details on individual study design, methods of recruitment, sampling frame,

sample size, location, response rate, analysis performed, results, confounders, reported HIV prevalence/incidence and self-reported sexual behaviour, HIV prevalence/incidence and self-reported sexual behaviour in comparison groups (if provided).

Analysis

First, a critical appraisal of the quality of each individual efficacy study was performed by two researchers (SS, MS) using a checklist approach to assess the methodological components [26]. In the next step a compilation was done, including all relevant studies or reviews for each intervention. The data compilations were then reviewed by SS and MS, together with a senior researcher (AT), in order to check for consistency. Implementation studies were appraised for availability, acceptability, uptake, feasibility of implementation, implementation costs, and (when available) effectiveness of the intervention among MSM in the European setting.

A paucity of implementation data was found in the EU/EEA setting. Therefore the HASTE grading framework was adjusted slightly regarding grade 2b. Interventions with limited efficacy data, defined as being plausible but lacking European implementation data were assigned a grade 2b. Interventions without established efficacy were assigned a grade 2c in order to differentiate interventions with (grade 2b) and without (grade 2c) established efficacy.

The evidence gathered for each intervention was reviewed using the HASTE grading framework [20]. The grading was performed independently by two researchers (SS and MS) and showed high agreement (90%). All grades were reviewed by a senior scientist (AT) and discrepancies were discussed initially in the smaller group, and following that in a conference with the co-authors (SS, MS, AP, FH, SB, AT) where remaining discrepancies and questions were resolved. Biological and public health plausibility was determined through a process of discussions within the team of co-authors.

Results

Twenty-four HIV prevention interventions for MSM were included and reviewed. Table 2 presents the intervention topics as well as the number of articles found through search strategies, screened and included per intervention.

Interventions assigned a strong recommendation (HASTE grade 1)

Four interventions were assigned a HASTE grade 1: condom use, universal coverage of antiretroviral treatment and treatment as prevention, peer-led group interventions and peer outreach within the MSM community.

Condom use

Consistent efficacy data showed that condom use during anal intercourse prevents HIV transmission. A systematic review including five cohort studies (n=8,825) reported that condom use reduced HIV transmission (relative risk (RR): 0.36; 95% confidence interval (CI) 0.20–0.67) [27-32]. Implementation data supported acceptability and feasibility of condom use among MSM and the feasibility of condom distribution programmes in Europe [33-35]. Thirteen per cent of MSM in European countries reported they had UAI in the last 12 months solely because they did not have a condom available, which points towards an unmet need of condoms among some MSM [36]. Plausibility was determined as condoms are a barrier method, thereby preventing the transmission of HIV. No serious potential risk with using condoms was identified.

Universal coverage of antiretroviral treatment and treatment as prevention

A randomised, double-blinded controlled trial with 1,763 serodiscordant heterosexual couples and 37 serodiscordant male MSM couples, reported a relative reduction of 96% in the number of linked HIV-1 transmissions cases resulting from the early initiation of antiretroviral therapy, as compared with delayed therapy. Since only 37 MSM couples were included, the size of the relative reduction reported may not accurately reflect the protective effect on sexual transmission between MSM. Implementation data reports that ART programmes are available in all EU/EEA countries. However, national treatment guidelines show diversity regarding when to start treatment (at diagnosis or at $CD4$ count threshold level) [10]. Plausibility was deemed high as ART decreases the replication of HIV-1 and has been shown to reduce the amount of HIV-1 in genital secretions [37], which is likely to be the mechanism by which antiretroviral treatment reduces sexual transmission of the virus among MSM. However, the effectiveness of this intervention is dependent on comprehensive HIV testing programmes among MSM, and effective linkage to and retention in high-quality HIV treatment and care.

Peer-led group interventions

Peer-led group interventions, defined as interactive group activities where a trained peer facilitates promotion of precautionary behaviours for HIV, were found to cause a significant reduction in UAI by a systematic review including 21 studies (n=5,197 and one study of unknown sample size) [38]. The size of the reduction ranged from 13% to 33% [38-40]. Implementation data show high uptake of peer-led group interventions among MSM in Europe [38,41]. The intervention was judged plausible as the effect of peer-led group interventions may decrease high-risk behaviours for HIV through a combination of increased knowledge, social learning, influence of peers and normative group behaviour [38].

Peer-outreach

A review of systematic reviews that included 4 reviews (in total including 11 studies with n›7,890) found that peer outreach interventions, where a trained peer approaches MSM in community settings providing

Table 3a

Highest Attainable Standard of Evidence (HASTE) evaluation per HIV prevention intervention in men who have sex with men in Europe

Intervention	Outcome	Efficacy data	Implementation data	Plausibility	Grading
		Consistent/limited/inconsistent/NA	Available/NA from European setting	Biological plausibility /Public health plausibity	HASTE grade 1–4
Condom use	HIV incidence	Efficacy data are consistent. A systematic review from 2010 including five cohort studies (n=8,825) reports that the overall effect of condom use on HIV transmission was RR: 0.36; 95% CI 0.20–0.67, consistent condom use was found to reduce HIV transmission by 64% [27-32].	Available. Distribution of condoms is feasible. High acceptability and feasibility of condom use has been reported among MSM [33-35]	The intervention has biological plausibility. The condom acts as barrier, thereby preventing the transmission of HIV. No serious potential risk with using condoms has been identified. Operations research emphasises the importance of condom-compatible lubricant use at condom use during anal sex [120].	Strong, grade 1
Universal coverage of antiretroviral treatment and treatment as prevention	HIV incidence	Efficacy is consistent [37, 121-124]. A randomised, double-blinded controlled trial with 1,763 serodiscordant heterosexual couples and 37 serodiscordant male MSM couples, reported a relative reduction of 96% in the number of linked HIV-1 transmission cases resulting from the early initiation of ART, as compared with delayed therapy [37].	Available. Implementation data reports that ART programmes are available in all EU/EEA countries. However, national treatment guidelines show diversity regarding when to start treatment (at diagnosis/CD4 count threshold level) [10, 121-124].	The intervention has biological plausibility. ART decreases the replication of human immunodeficiency virus type 1 and has been shown to reduce the amount of HIV-1 in genital secretions [37], the likely mechanism for how ART reduces sexual transmission of the virus among MSM. A consideration is the reported low rates (43–84%) of ever having tested for HIV among European MSM, limiting the effect of serostatus-dependent prevention interventions [125].	Strong, grade 1
Peer-led group interventions	UAI	Efficacy data are consistent. A systematic review including 21 studies (n=5,197 and one study on unknown sample size) found a significant reduction in UAI. The size of the reduction ranged from 13% to 33% [38-40].	Available. Implementation data are consistent and show high uptake of peer-led group interventions [33, 38].	Peer-led group interventions for MSM have public health plausibility. Acceptability and uptake might be improved by the involvement of peers creating enabling and safe environments for MSM to provide information and counselling.	Strong, grade 1
Peer outreach	UAI	Efficacy data are consistent. A systematic review including 11 studies (n>7,890) reports that peer-led outreach interventions are effective in reducing UAI. Three meta-analysis reports significant reduction in UAI (OR: 0.7; 95% CI 0.49–0.99; OR: 0.65; 95% CI 0.48–0.89), RR: 0.70; 95% CI 0.55–0.91) in comparison with no HIV prevention [38].	Available. Peer outreach is common and generally well-received among MSM in Europe [10].	Peer outreach has public health plausibility through that peers can serve as a first point of interaction to create an enabling environment were persons who may not seek prevention interventions can be reached and introduced to such interventions.	Strong, grade 1
Voluntary testing and counselling for HIV	Condom use	Efficacy data are limited. A systematic review including 11 studies (n=4,416, of which 418 MSM), where six studies compared PLWH aware of their status with PLWH unaware of their status and five studies compared individuals before and after seroconverting. The data concluded that high-risk sexual behaviour for HIV is reduced after becoming aware of living with HIV, reduction in UAI ranged from 25% to 65%. No reduction was seen among those testing negative. Among MSM living with HIV, studies report increased condom use and decrease in number of sexual partners following HIV diagnosis [42-45].	Available. Acceptability for testing was found to be high, EMIS reports that the national proportion of MSM reporting having had an HIV-test during the past 12 months ranged from 20% to 47%, with a median of 37% [35, 46-48].	The intervention has biological plausibility, VCT may influence behaviour change through a process involving acquisition of HIV/AIDS knowledge and learning one's HIV serostatus [26]. Knowledge of HIV status enables access to treatment and prevention efforts dependent on HIV serostatus.	Probable, grade 2a

ART: antiretroviral therapy; CI: confidence interval; EEA: European Economic Area; EMIS: European MSM Internet survey; EU: European Union; FTC–TDF: emtricitabine and tenofovir ; LGBTI: lesbian, gay, bisexual, transgender and intersex; MSM: men who have sex with men; NA: not available; OR: odds ratio; PEP: post-exposure prophylaxis; PrEP: pre-exposure prophylaxis; PLWH: people living with HIV; RCT: randomised controlled trial; RR: relative risk; UAI: unprotected anal intercourse; US: United States; VCT: voluntary testing and counselling.

Table 3b

Highest Attainable Standard of Evidence (HASTE) evaluation per HIV prevention intervention in men who have sex with men in Europe

Intervention	Outcome	Efficacy data	Implementation data	Plausibility	Grading
		Consistent/limited/inconsistent/NA	Available/NA from European setting	Biological plausibility /Public health plausibity	HASTE grade 1–4
Condom-compatible lubricant use	Condom failure	Efficacy data are limited. Lack of additional lubricants during anal intercourse has been associated with condom failure [49-52]. A study investigating usage of 915 condoms at anal intercourse reported a reduction in slippage and breakage when using lubricants [53]. Oil-based lubricants (not condom-compatible) have been shown to decrease tensile strength and increase permeability in latex condom and thereby increase breakage rates [50,51].	Available. Studies have showed that use of lubricants among MSM is common. Distribution of condom compatible lubricants is feasible [54-55].	The intervention has biological plausibility, decreasing the amount of condom failure as well as the amount of micro-tears in rectum of the receptive partner by using condom-compatible lubricants at anal sex might provide a protective effect for HIV transmission [54-56].	Probable, grade 2a
Post-exposure prophylaxis	HIV incidence	Efficacy data are limited. Two retrospective cohort studies of patients receiving PEP in Denmark (n=374) and Amsterdam (n=189) have been performed, each study reported one seroconversion [57-58]. No adherence data was found.	Available. Implementation data reports a low demand for PEP in some European settings, the national proportion of MSM who have ever taken PEP ranged from 0% to 3.4% with a country median of 1.3% [36,57-58].	The intervention has a high biological plausibility. ART is highly effective in preventing the HIV-1 virus to replicate, thereby removing any virus before it can establish an infection. However, a low demand has been noticed in some European settings, which might decrease the public health plausibility, and information and availability might need to be strengthened.	Probable, grade 2a
Individual counselling for MSM living with HIV	UAI	Efficacy data are limited. A cohort study with one intervention (n=146 MSM) and one control arm (n=180) reported a significant decrease in UAI among MSM with ≥2 sex partners. A study comparing counselling vs standard of care in a primary-care setting found no difference regarding UAI at six-month follow-up. A RCT of peer-led individual counselling intervention reported a decline in HIV transmission at 6- and 12-month follow-up (n=249) [59-61].	Available. Implementation data report that acceptability and uptake of individual counselling is high [60-61].	Counselling for MSM living with HIV has biological plausibility, through a process where increased knowledge may lead to behaviour change reducing the risk of HIV transmission and risk of acquiring STIs, which might increase viral load and accelerate disease progression [62]. The benefit of episodic or one-time intervention was subject to decay over time and it would need boosters to maintain its effect.	Probable, grade 2a
Individual counselling for MSM	UAI	Efficacy data are inconsistent. A systematic review found inconsistent evidence regarding the effectiveness of counselling interventions in reducing UAI among MSM (n=11,636) [38]. Two meta-analysis report that HIV counselling (from studies with a comparison group receiving standard of care) was significantly associated with a reduction in UAI (OR: 0.59; 95% CI 0.36–0.97 n=2339; OR: 0.57; 95% CI 0.37–0.87 n=4689) [39,40]. Another meta-analysis found the absolute effects (from studies with a wait list control group) to show a non-significant reduction in UAI (RR: 0.80; 95% CI 0.60–1.06) [63].	Available. HIV counselling interventions are reported to be acceptable and feasible among MSM in Europe [36].	Interventions to increase knowledge of HIV and prevention measures have public health plausibility as they can influence behaviour change [126].	Possible, grade 2b

ART: antiretroviral therapy; CI: confidence interval; EEA: European Economic Area; EMIS: European MSM Internet survey; EU: European Union; FTC–TDF: emtricitabine and tenofovir ; LGBTI: lesbian, gay, bisexual, transgender and intersex; MSM: men who have sex with men; NA: not available; OR: odds ratio; PEP: post-exposure prophylaxis; PrEP: pre-exposure prophylaxis; PLWH: people living with HIV; RCT: randomised controlled trial; RR: relative risk; UAI: unprotected anal intercourse; US: United States; VCT: voluntary testing and counselling.

Table 3c

Highest Attainable Standard of Evidence (HASTE) evaluation per HIV prevention intervention in men who have sex with men in Europe

Intervention	Outcome	Efficacy data	Implementation data	Plausibility	Grading
		Consistent/limited/inconsistent/NA	Available/NA from European setting	Biological plausibility /Public health plausibity	HASTE grade 1–4
Peer-led group interventions targeting MSM living with HIV	UAI	Efficacy data are limited. A study comparing a five-session group intervention focusing on promoting safe sex (n=97) with a five-session standard of care support group (n=77) reports a decrease in UAI among participants [64]	NA	Public health plausibility was determined. The effect of peer-led group interventions may improve uptake of intervention and promote safe sex behaviour through a combination of increased knowledge, social learning, influence of peers and normative group behaviour [38].	Possible, grade 2b
Internet-based HIV prevention messages	UAI	Efficacy data are inconsistent. An RCT of a persuasive computing interactive intervention has shown a reduction of UAI at three months but could not maintain the effect at 12-month follow-up [65]. An RCT that evaluated the short-term efficacy (60 days) of a low intensity digital media intervention found significant reductions in UAI among men exposed to videos or to a website [57]. Two RCT report no differences in UAI between intervention and control groups [67-68].	NA	Interventions that increase knowledge on HIV and prevention measures have biological plausibility. Internet is one of the largest venues where MSM meet sexual partners [69,70]. Thereby messaging on the Internet would potentially reach a large number of MSM. In addition, safe-sex messaging on the venue where MSM meet sex partners could influence normative behaviour around safe sex.	Possible, grade 2b
Interventions in sex-on-premises venues	UAI and uptake of HIV testing	Efficacy data are limited. A study performing a VCT intervention at a bathhouse tested 133 men, of whom 48% had not been tested in the previous 12 months. A decrease in UAI was reported three months after the intervention [73-75].	NA	Sex venue-based interventions have public health plausibility through creating easy access to prevention interventions at the location where men meet sex partners, possibly reaching MSM who do not visit service sites [76,77]. Programmes may create social norms that can impact how MSM negotiate around sexual behaviour at sex venues [127,128] [47].	Possible, grade 2b
Social marketing interventions	Uptake of HIV-testing	Efficacy data are limited. A systematic review including three studies of cross-sectional design before and after the intervention reports a significant increase in HIV-testing uptake (OR: 1.58; 95% CI 1.40–1.77) [78].	NA	Social marketing interventions have public health plausibility through increasing knowledge on HIV and prevention measures and services. Awareness campaigns can also spark discussions and strengthen awareness, which can create a change in social norms.	Possible, grade 2b
Pre-exposure prophylaxis[a]	HIV incidence	Efficacy data are limited. One multicentre RCT, iPrEx, shows a 44% reduction in the incidence of HIV (95% CI 15–63; p=0.005) during a 3,324 person-years follow-up period among MSM. Detectable FTC–TDF blood levels strongly correlated with the prophylactic effect, emphasising the importance of adherence to PrEP [83].	NA	The intervention has biological plausibility. See section for PEP. Little is known about potential long-term side effects, adherence and drug resistance.	Possible, grade 2b

ART: antiretroviral therapy; CI: confidence interval; EEA: European Economic Area; EMIS: European MSM Internet survey; EU: European Union; FTC–TDF: emtricitabine and tenofovir ; LGBTI: lesbian, gay, bisexual, transgender and intersex; MSM: men who have sex with men; NA: not available; OR: odds ratio; PEP: post-exposure prophylaxis; PrEP: pre-exposure prophylaxis; PLWH: people living with HIV; RCT: randomised controlled trial; RR: relative risk; UAI: unprotected anal intercourse; US: United States; VCT: voluntary testing and counselling.

[a] New data have been published during 2015 providing implementation data for PrEP [115, 116].

[b] Assigned possible, grade 2b, for MSM who are only or mostly insertive during intercourse.

Table 3D

Highest Attainable Standard of Evidence (HASTE) evaluation per HIV prevention intervention in men who have sex with men in Europe

Intervention	Outcome	Efficacy data	Implementation data	Plausibility	Grading
		Consistent/limited/ inconsistent/NA	Available/NA from European setting	Biological plausibility / Public health plausibity	HASTE grade 1–4
Voluntary medical male circumcision[b]	HIV incidence	Efficacy data are consistent among men primarily or exclusively being insertive at anal sex. A Cochrane comprehensive review of 21 observational studies with a total of 71,693 participants found insufficient evidence that male circumcision prevents acquisition of HIV among MSM. Among men having primarily or exclusively insertive anal sex, a significant decrease in HIV infection was found (OR:0.27; 95% CI 0.17–0.44) [84]. A longitudinal study reports a reduced risk of HIV acquisition by 69% among MSM who reported ≥60% of acts as insertive with their last three sex partners) [85].	NA	The intervention has a biological plausibility among MSM who are only or mostly insertive during anal intercourse [85,130-133].	Possible, grade 2b
Training for healthcare providers to offer comprehensive care for MSM	NA	NA	NA. Many published and online resources are available to train health providers about issues facing MSM [7].	Training for providers to offer comprehensive care for MSM has public health plausibility. With adequate education and training, healthcare providers can provide appropriate routine care for MSM patients and help patients to avoid internalising stigma associated with homosexuality, prevent HIV acquisition, reduce unsafe sex, and lead more satisfying and healthy lives [7].	Pending, grade 2c
MSM-competent clinics	NA	NA	Available. MSM clinics that offer comprehensive services to MSM are available in many European metropolitan areas and have demonstrated high uptake of their services [86].	MSM-friendly clinics that offer comprehensive services have biological plausibility through removing barriers that stop MSM from seeking care or from disclosing relevant personal information once in care [87].	Pending, grade 2c
Voluntary anonymous partner notification	HIV incidence	NA	Available. Acceptability, defined as willingness of index patients to notify their sex partners, has been shown to be high among MSM in Europe [88,89].	Contract tracing has biological plausibility by enabling early diagnosis, treatment and care, which benefits the individual person as well as likely interrupting the transmission chain, thereby reducing incidence.	Pending, grade 2c
Campaigns for lesbian, gay, bisexual, transgender and intersex equality	Self-reported stigma towards LGBTI	No studies have fully evaluated structural interventions for MSM. Education programmes focusing on changing straight-identified persons' perceptions and challenging gender norms have been shown to be successful in decreasing stigma [90,91].	NA	Anti-stigma and LGBTI rights promotion has public health plausibility by removing structural barriers and providing a climate where MSM can access preventive service without fear of stigma [134].	Pending, grade 2c

ART: antiretroviral therapy; CI: confidence interval; EEA: European Economic Area; EMIS: European MSM Internet survey; EU: European Union; FTC–TDF: emtricitabine and tenofovir ; LGBTI: lesbian, gay, bisexual, transgender and intersex; MSM: men who have sex with men; NA: not available; OR: odds ratio; PEP: post-exposure prophylaxis; PrEP: pre-exposure prophylaxis; PLWH: people living with HIV; RCT: randomised controlled trial; RR: relative risk; UAI: unprotected anal intercourse; US: United States; VCT: voluntary testing and counselling.

[a] New data have been published during 2015 providing implementation data for PrEP [115, 116].

[b] Assigned possible, grade 2b, for MSM who are only or mostly insertive during intercourse.

Table 3e

Highest Attainable Standard of Evidence (HASTE) evaluation per HIV prevention intervention in men who have sex with men in Europe

Intervention	Outcome	Efficacy data	Implementation data	Plausibility	Grading
		Consistent/limited/ inconsistent/NA	Available/NA from European setting	Biological plausibility /Public health plausibity	HASTE grade 1–4
Female condom use at anal sex	Condom failure	Further evidence is needed to establish efficacy. One study reports no significant difference regarding condom breakage at anal sex compared with male condoms, but a higher rate of condom slippage OR: 2.7; 95% CI 1.2–5.8) (n=76) in comparison to male condoms [92].	NA	The intervention has biological plausibility as a barrier method. Female condoms potentially offer a protection method controlled by the receptive partner at anal sex. Higher rates of slippage, pain and discomfort when using the female condom at anal sex has been reported compared with using male latex condoms which is a potential risk/harm with female condom use at anal sex [92]. There is a need for safety and efficacy studies of a female condom designed for anal sex.	Pending, grade 2c
Serosorting	HIV incidence	Efficacy data are inconsistent. A systematic review included three observational studies found that serosorting increased HIV transmission by 79% compared with condom use [27]. However, compared with no condom use serosorting reduced HIV transmission by 53% [27,93]. The Explore trial performed among MSM in six US cities found that serosorting was associated with a modest reduction in HIV acquisition for HIV-negative MSM (OR: 0.88; 95% CI 0.81–0.95) [94].	NA. European men have reported in studies that they use serosorting as a risk management approach [95,96].	Serosorting may not have an effect due to low testing rates and the low possibility of detecting primary HIV infection. Public health plausibility is undefined, There is a risk that individuals may rely on a negative HIV-testing result that is not accurate.	Insufficient, grade 3
Avoiding semen in the mouth/ unprotected oral sex	HIV incidence	Efficacy data are inconsistent. One prospective cohort study including 2,189 high risk MSM in the US between 1992 and 1994 (2,633 person-years) reports a 0.06% risk of HIV at receptive oral sex with a sexual partner living with HIV and a 0.04% (95% CI 0.01–0.17) risk with a sexual partner. A cross-sectional study including 239 MSM reporting only having oral sex over the past six months (1999–2001) detected no cases of HIV. Observational studies from several high-income country settings have reported cases of self-reported oral transmission of HIV [102, 135-137].	NA	There is biological plausibility that not taking semen in the mouth and thereby limiting the contact between semen with possible HIV virus content and the oral mucosa could potentially remove this opportunity for transmission. However, transmission rates reported are between 0% and 0.04%, which is lower than estimated per contact risk of HIV at receptive anal intercourse with a condom (0.18%; 95% CI 0.10–0.28%). The low risk of HIV transmission implies that the avoidance of taking semen in the mouth would not have any significant effect.	Insufficient, grade 3

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Table 3f

Highest Attainable Standard of Evidence (HASTE) evaluation per HIV prevention intervention in men who have sex with men in Europe

Intervention	Outcome	Efficacy data	Implementation data	Plausibility	Grading
		Consistent/limited/ inconsistent/NA	Available/NA from European setting	Biological plausibility /Public health plausibity	HASTE grade 1–4
Avoiding nitrite inhalants/poppers at UAI	NA	NA	NA. Consistent high usage of poppers across European settings was self-reported in the EMIS 2010 study [35].	The pathway by which nitrite inhalants could lead to transmission of HIV is unclear. Nitrites inhalants cause peripheral vasodilatation and are believed to decrease anal sphincter tone, potentially leading to more traumatic sexual intercourse or more direct exposure to HIV target cells [98]. There are limited animal and human data suggesting that nitrite inhalants may cause transient immunosuppression or alter cytokine profiles, which could enhance transmission of HIV across mucosal barriers [99, 100]. Nitrite inhalants have been reported to be associated with high-risk sexual behaviour for STI/HIV including higher number of partners [101-103]. Frequent use of sex drugs may imply a high-risk marker of behavioural disinhibition that includes receptive UAI with multiple partners [98,104]. Limited evidence supporting biological plausibility was found.	Insufficient, grade 3
Interventions to reduce alcohol binge drinking	UAI	Efficacy data are inconsistent. A RCT study evaluated a combined intervention among MSM living with HIV promoting two target behaviours, abstinence from/ reduction in alcohol use and safe sex practices, compared with an unexposed control group reports no effect on UAI (n=253) [105].	NA	There is plausibility that alcohol binge drinking through disinhibition can lead to increased sexual risk behaviour [138]. Thus, behavioural interventions that decrease alcohol consumption might lead to decrease in UAI.	Insufficient, grade 3

ART: antiretroviral therapy; CI: confidence interval; EEA: European Economic Area; EMIS: European MSM Internet survey; EU: European Union; FTC–TDF: emtricitabine and tenofovir ; LGBTI: lesbian, gay, bisexual, transgender and intersex; MSM: men who have sex with men; NA: not available; OR: odds ratio; PEP: post-exposure prophylaxis; PrEP: pre-exposure prophylaxis; PLWH: people living with HIV; RCT: randomised controlled trial; RR: relative risk; UAI: unprotected anal intercourse; US: United States; VCT: voluntary testing and counselling.

information and peer support, are associated with a 30% reduction in UAI compared with minimal or no HIV prevention [38]. Peer outreach is common and generally well-received among MSM in Europe [10]. The intervention was judged plausible as peers can serve as a first point of interaction to create an enabling environment were persons who may not seek prevention interventions can be reached and introduced to interventions such as counselling, HIV/STI testing and treatment.

Interventions assigned a probable recommendation (HASTE grade 2a)

HASTE grade 2a was assigned to four interventions: Voluntary counselling and testing for HIV, condom-compatible lubricant, post-exposure prophylaxis (PEP), and individual counselling for MSM living with HIV.

Voluntary testing and counselling for HIV

A systematic review performed in 2005 including 11 studies (n=4,416, of which 418 MSM), where six studies compared PLWH aware of their status with PLWH unaware of their status, and five studies compared individuals before and after seroconverting. The data concluded that high-risk sexual behaviour for HIV is reduced after becoming aware of living with HIV, reduction in UAI ranged from 25% to 65%, but no reduction was seen among those testing negative. Among MSM living with HIV, studies report increased condom use and decrease in number of sexual partners following HIV diagnosis and counselling [42-45].

Acceptability for testing was found to be high, EMIS reports that the national proportion of MSM reporting having had an HIV-test during the past 12 months ranged from 20% to 47%, with a country median of

37%. However, the proportion that were 'quite' or 'very' confident they could access an HIV test if they wanted one ranged from 73% to 96% with a median of 91% [35,46-48]. Plausibility was determined as VCT may influence behaviour through a process involving acquisition of HIV/AIDS knowledge and learning one's HIV serostatus [45]. In addition, knowledge of HIV status enables access to ART and care, reducing onward transmission.

Condom-compatible lubricant use

Lack of additional lubricants during anal intercourse has been associated with condom failure [49-52]. A study investigating usage of 915 condoms at anal intercourse reported a reduction in slippage and breakage when using lubricants [53]. However, oil-based lubricants (not condom-compatible) have been shown to decrease tensile strength and increase permeability in latex condom and increase breakage rates [50,51]. Implementation data reports that lubricant use among MSM is high [36]. The intervention was judged plausible by the decrease in condom failure as well as that the amount of micro-tears in rectum of the receptive partner may be diminished by using condom-compatible lubricants [54-56].

Post-exposure prophylaxis

PEP, defined as the administration of ART starting within 72 hours post exposure and prolonged for 28 days, was evaluated by two retrospective cohort studies of patients receiving PEP in Denmark (n=374) and Amsterdam (n=189), each study reported one seroconversion [57,58]. No adherence data were found. Implementation data reports a low demand for PEP in some European settings, although it is considered the standard of care. The national proportion of MSM who have ever taken PEP ranged from 0% to 3.4% with a country median of 1.3% [36]. Low demand and uptake limit the public health impact of PEP. Information about and availability of PEP might need to be strengthened [57,58]. Plausibility is determined by the effect of ART post-exposure (within 72 hours) that diminishes the HIV-virus before an infection can be established.

Individual counselling for men who have sex with men living with HIV

A cohort study comparing an intervention group receiving individual counselling on risk reduction for HIV by a trained counsellor (n=146) and one control group (n=180) reported a significant decrease in UAI among MSM living with HIV with more than two sexual partners. Another RCT of peer-led individual counselling intervention reported a decline in sexual risk behaviour for HIV at 6 and 12 months follow-up (n=249) [59-61]. Implementation data report that acceptability and uptake of individual counselling are high [60,61]. Plausibility is determined through a process where increased knowledge may lead to behaviour change reducing the risk of HIV transmission and risk of acquiring STIs that might increase viral load and accelerate disease progression [62].

Interventions assigned a possible recommendation (HASTE grade 2b)

An additional seven interventions were graded HASTE grade 2b including: individual counselling for MSM, peer-led group interventions targeting MSM living with HIV, Internet-based HIV prevention messages, interventions in sex-on-premises venues, social marketing interventions, pre-exposure prophylaxis (PrEP) and voluntary medical male circumcision.

Individual counselling for men who have sex with men

Two meta-analyses examining individual counselling on HIV risk reduction with a comparison group receiving standard care found significant 41% and 43% reductions in UAI (OR: 0.59; 95% CI 0.36–0.97, n=2,339; OR: 0.57; 95% CI 0.37–0.87, n=4,689) [39,40]. A recent systematic review which included both these studies reports inconsistent evidence regarding the effectiveness of individual counselling in reducing UAI among MSM (n=11,636) [38]. This is due to the inclusion of another meta-analysis that found individual counselling clients (compared with waiting list control group) to report a non-significant 20% reduction in UAI (RR: 0.80; 95% CI 0.60–1.06) [63]. HIV counselling interventions are reported to be acceptable and feasible among MSM in Europe [36]. Plausibility is defined as interventions that increase knowledge of HIV and prevention measures can influence behaviour change.

Peer-led group interventions targeting men who have sex with men living with HIV

Peer-led group interventions among MSM living with HIV are defined as interactive group activities facilitated by a trained peer. A study comparing a five-session group intervention focusing on promoting safe sex (n=97) with a five-session standard of care support group (n=77) reports a decrease in UAI among participants [64]. Implementation data were not available. Plausibility was determined as the effect of peer-led group interventions may improve uptake by creating enabling and safe environments for MSM and promote safe sex behaviour through a combination of increased knowledge, social learning, influence of peers and normative group behaviour [38].

Internet-based HIV prevention messages

The Internet is a special venue in the sense that apart from being another potential meeting-dating venue, it may also be a venue for private and anonymous access to sexual health and well-being, at your own choice of time and physical place. Since specific longitudinal online interventions exist that are exclusively for use on the Internet, it was deemed important to review Internet-based interventions separately from other sex-venue based interventions.

An RCT of a persuasive computing interactive HIV messaging intervention has shown a reduction of UAI at three-month follow-up, but could not maintain the effect at 12-month follow-up [65]. An RCT that evaluated the short-term efficacy (60 days) of a low-intensity

digital media HIV messaging intervention found significant reductions in UAI among men exposed to videos or to a website [66]. Two RCTs report no differences in UAI between an intervention group receiving Internet-based messaging and non-exposed control groups [67,68]. The Internet is a common setting for MSM to meet sexual partners [69-72]. Messaging on the Internet would potentially reach a large number of MSM. The intervention was judged plausible as safe sex messaging on the online venue where MSM meet sex partners could influence normative behaviour around safer sex practices.

Interventions in sex-on-premises venues

Interventions in sex-on-premises venues are defined as prevention activities such as information, counselling and VCT at venues where MSM gather and seek sexual partners. A VCT intervention at a bathhouse tested 133 men of whom 48% had not been tested in the previous 12 months. A decrease in UAI was reported 3 months after the intervention, which highlights the prevention effect of HIV testing among those never tested before [73-75]. Implementation data were not available. Sex venue-based interventions have public health plausibility through creating easy access to prevention interventions at a location where MSM gather and meet sex partners, possibly reaching MSM who do not visit service sites [76,77].

Social marketing interventions

A systematic review of social marketing strategies promoting HIV testing (including three intervention evaluations of cross-sectional before-and-after design) reports a significant increase in HIV-testing uptake (OR: 1.58; 95% CI 1.40–1.77) [78]. Social marketing interventions include media messaging (any form of media) grounded in social marketing theory [79-82]. Implementation data were not available. Public health plausibility is achieved through increasing knowledge of HIV and prevention measures and services, through manipulation of perceptions of the desirability of precautions (and the undesirability of risks) and through the promotion of social norms for precaution.

Pre-exposure prophylaxis

One multicentre RCT, iPrEx, evaluated the efficacy of once-daily oral emtricitabine and tenofovir (FTC–TDF, Truvada) among men and transgender women who have sex with men (n=1,251) compared with placebo (n=1,224) for the prevention of HIV acquisition. One hundred people became infected during the follow-up period of 1.8 years (median, 1.2 years; maximum, 2.8 years, total of 3,324 person-years). Thirty six in the FTC–TDF group and 64 in the placebo group became infected, which indicates a 44% reduction in the incidence of HIV (95% CI 15–63; p=0.005). In the FTC–TDF group, the study drug was detected in 22 of 43 of seronegative subjects (51%) and in 3 of 34 HIV-infected subjects (9%) (p<0.001) [83]. Detectable FTC–TDF blood levels strongly correlated with the prophylactic effect, emphasising the importance of adherence to PreP. Little is known about potential long-term side effects, adherence, impact on other risk behaviour and drug resistance. Biological plausibility is determined; ART is highly effective in preventing replication of the HIV-1 virus, and so its presence could remove any virus before an infection can be established.

Voluntary medical male circumcision

A Cochrane comprehensive review of 21 observational studies with a total of 71,693 participants found insufficient evidence that male circumcision prevents acquisition of HIV among MSM [84]. However, among men having primarily or exclusively insertive anal sex, there was a significant decrease in HIV infection (OR: 0.27; 95% CI 0.17–0.44) [84]. The longitudinal study suggested that it reduced risk of HIV acquisition by 69% among MSM who reported ≥60% of acts as insertive with their last three partners [85]. Programmatic issues such as safety of male circumcision, sexual behaviour following male circumcision, and sexual satisfaction and function have not been addressed specifically among MSM. No implementation data were found. The effect is plausible among MSM who are only or mostly insertive during anal intercourse, which would comprise a limited group of MSM. Therefore, the intervention receives a grade of 2b for MSM who are only or mostly insertive during anal intercourse.

Interventions assigned a pending recommendation (HASTE grade 2c)

A HASTE grade 2c was assigned to five interventions: training for healthcare providers to offer comprehensive care for MSM, MSM-competent health clinics, voluntary anonymous partner notification, campaigns for lesbian, gay, bisexual, transgender and intersex equality (LGBTI), and female condom use for anal intercourse.

Training for healthcare providers to offer comprehensive care for men who have sex with men

Published and online resources are available to train health providers about issues facing MSM, but no evaluation study was found [7]. Implementation data were not available. Plausibility was deemed strong because training providers can offer comprehensive care for MSM, including appropriate routine care for MSM patients, and help patients to avoid internalising stigma associated with homosexuality, prevent HIV and other STI acquisition, and lead more satisfying and healthy lives [7].

MSM-competent health clinics

MSM-competent health clinics that offer comprehensive services to MSM are available in many European metropolitan areas and have demonstrated high uptake of their services [86]. MSM-competent health clinics that offer comprehensive services have plausibility through removing barriers that prevent MSM from seeking care or from disclosing relevant personal information once in care [87].

Voluntary anonymous partner notification

No studies evaluating voluntary anonymous partner notification were found. Acceptability, defined as willingness of index patients to notify their sex partners about living with HIV, has been shown to be high among MSM in Europe [88,89]. Voluntary anonymous partner notification has a plausible effect by enabling early diagnosis, treatment and care, which benefits the individual person as well likely interrupting the transmission chain, thereby reducing HIV incidence.

Campaigns for lesbian, gay, bisexual, transgender and intersex equality

No studies have fully evaluated structural interventions for MSM defined as activities promoting equality through education, media awareness campaigns and policy regarding an HIV-preventative effect. Education programmes focusing on changing straight-identified men and women's perceptions of the heterosexual majority and challenging gender norms have been shown to be successful in decreasing stigma against LGBTI [90,91]. Implementation data are not available. Anti-stigma and LGBTI rights promotion have public health plausibility by removing structural barriers and providing a climate where MSM can access preventive and care service without fear of stigma.

Female condom use for anal intercourse

In comparisons with male condoms, one study reports the female condom to have no significantly different breakage at anal intercourse, but to have a higher rate of slippage OR: 2.7; 95% CI 1.2–5.8 (n=76) [92] No implementation data from Europe were found. The intervention has plausibility as a barrier method for HIV transmission. Female condoms potentially offer a protection method controlled by the receptive partner at anal intercourse. Higher rates of slippage, pain and discomfort when using the female condom at anal intercourse have been reported compared with using male latex condoms, which is a potential risk/harm with female condom use at anal intercourse [92]. There is a need for safety and efficacy studies of a female condom developed particularly for anal intercourse.

Interventions assigned an insufficient recommendation (HASTE grade 3)

An insufficient level of evidence available, HASTE grade 3, was assigned to four interventions: serosorting, avoiding taking semen in the mouth/unprotected oral sex, avoiding use of poppers at UAI and avoiding alcohol binge drinking.

Serosorting

A systematic review including three observational studies [27] found that serosorting (i.e. only engaging in unprotected intercourse with individuals thought to have the same HIV status), increased HIV transmission by 79% compared with condom use. However, compared with no condom use, serosorting reduced HIV transmission by 53% [27, 93]. The Explore trial performed among MSM in six cities in the United States (US) found that serosorting was associated with a modest reduction in HIV acquisition for HIV-negative MSM (OR: 0.88; 95% CI 0.81–0.95) [94]. Some European men have reported in studies that they use serosorting as a risk management approach [95, 96]. Serosorting may not have an effect due to low testing rates and the low possibility of detecting primary HIV infection. There is a risk that individuals may rely on a negative HIV test result that is not accurate. Serosorting among people living with HIV can be associated with an increased risk of STIs, which have been shown to cause a peak in HIV viral load in semen among individuals on ART, which could affect HIV onward transmission [97]. Public health plausibility is undefined.

Avoiding semen in the mouth/unprotected oral sex

A prospective cohort study including 2,189 high-risk MSM in the US between 1992 and 1994 (2,633 person years) reported a 0.06% risk of HIV at receptive oral sex with a sexual partner living with HIV and a 0.04% (95% CI 0.01–0.17) risk with a sexual partner of unknown serostatus [102]. A cross-sectional study including 239 MSM reporting only oral sex over the past six months (1999–2001) detected no HIV. No implementation data are available [136].

There is biological plausibility that not taking semen in the mouth and thereby limiting the contact between semen with possible HIV virus content and the oral mucosa could potentially remove this opportunity for transmission. However, transmission rates reported are between 0% and 0.04%, which is lower than estimated per contact risk of HIV at receptive anal intercourse with a condom (0.18%; 95% CI 0.10–0.28) The low risk of transmission implies that the avoidance of taking semen in the mouth would not have a significant effect on transmission [11].

Avoiding use of nitrite inhalants/poppers at unprotected anal intercourse

No efficacy data were available. Consistent high usage of poppers across European settings was self-reported in the EMIS 2010 study [36]. The pathway by which nitrite inhalants could lead to transmission of HIV transmission is unclear. Nitrite inhalants cause peripheral vasodilatation and are believed to decrease anal sphincter tone, potentially leading to more traumatic sexual intercourse or more direct exposure to HIV target cells [98]. There are limited animal and human data suggesting that nitrite inhalants may cause transient immunosuppression or alter cytokine profiles, which could enhance transmission of HIV across mucosal barriers [99,100]. Nitrite inhalants have been reported to be associated with high-risk sexual behaviour for STI/HIV including higher number of partners [101-103]. Frequent use of sex drugs may imply a high-risk marker of behavioural disinhibition that includes unprotected receptive anal intercourse with multiple partners [98,104]. Thereby, there is limited evidence supporting biological plausibility.

Interventions to reduce alcohol binge drinking

An RCT evaluated a combined intervention among MSM living with HIV promoting two target behaviours, abstinence from/reduction in alcohol use and safe sex practices, compared with an unexposed control group (n=253). The intervention had no effect on UAI [105]. Implementation data were not available. There is plausibility that alcohol binge drinking may cause disinhibition that can lead to increased sexual risk behaviour. Thus, behavioural interventions that decrease alcohol consumption might lead to a decrease in UAI.

Discussion

This systematic review of HIV prevention interventions among MSM found that four of the 24 interventions reviewed could be assigned a HASTE grade 1, equal to a strong recommendation. Another four interventions could be assigned grade 2a, equal to a probable recommendation. In addition, another seven interventions were assigned grade 2b, a possible recommendation. Unambiguous recommendations can be made to MSM to use condoms and condom-compatible lubricant when engaging in anal intercourse, to test frequently for HIV and STIs, to use ART if living with HIV, and, if uninfected, to use PEP if exposed to HIV. Recommendations can be made to service commissioners and providers to provide MSM with access to HIV testing, to provide medical care including ART to PLWH, to provide PEP to those not infected, and to provide or make otherwise accessible condoms and lubricant. Interventions which promote HIV testing, condom use, ART and PEP can also be recommended. Evidence-based delivery modes include peer-led interventions, educational outreach and group work programmes, with specific peer-led programmes for men living with HIV.

An important consideration in HIV prevention programme planning is that there are synergies and dependency between the recommended interventions, indicating that combining interventions into programmes is desirable [106]. For example, biomedical interventions dependent on HIV serostatus (e.g. ART, PrEP, PEP) need to be implemented in combination with easy access to the provision of VCT. An HIV-testing service itself can achieve high coverage through peer outreach and social marketing. Therefore, interventions should be packaged together to enhance their potential full effect to prevent HIV.

There was a striking lack of European effectiveness studies, where interventions are examined outside an RCT setting. Additional research into the areas of effectiveness in the European context is needed inform HIV prevention decision-making and programme planning. These are required both regarding new interventions, such as the implementation of PrEP programmes, and to report results of follow-up on already-implemented interventions such as early initiation of ART, PEP, and voluntary anonymous partner notification.

The challenge of scaling up ART for MSM with HIV in Europe includes both more widespread and more frequent HIV-testing, as well as increasing ART accessibility to men testing positive. In 2013, 37% of the MSM diagnosed with HIV in the EU/EEA were diagnosed late (defined as CD4 cell count<350/µL), indicating that many men who acquire HIV are unaware of their infection for some time [107]. Models using data from the 2010 United Kingdom national cohort of MSM living with HIV suggest that extending ART to MSM diagnosed with HIV with CD4 counts<500 cells/µL would have reduced the overall proportion of infectious men from 35% to 29%. However reducing the undiagnosed population by 50% would have reduced this to 21%, which serves to emphasise the importance of frequent HIV testing [108].

Comprehensive community education programmes linking peer community outreach work with easy access to HIV-testing and treatment are key components of universal coverage of antiretroviral treatment and treatment as prevention. As HIV self-tests become authorised for use in European countries, they may contribute to increased testing and linkage to care. A French study reported that accessing an unauthorised HIV self-test was associated with living one's sex life with men in total secrecy and having had unprotected anal intercourse with men during the last 12 months, indicating that for particular groups of MSM, autonomous self-testing may reduce barriers to testing [109]. The majority of literature on VCT included in this review was published before 2000, indicating a need for more contemporary published studies evaluating delivery of HIV testing among MSM in Europe.

Drug approval by the European Medicines Agency for emtricitabine and tenofovir disoproxil fumarate (TDF/FTC), brand-named Truvada, to be used for pre-exposure prophylaxis is currently pending. It has been approved by the US Food and Drug Administration since July 2012. Studies among MSM in France and the UK have showed a high interest in and acceptability for PreP among MSM [110,111]. Half of 842 HIV-negative MSM in London reported that they would consider using PrEP if it became available as a daily pill [111]. The long-term health effects of TDF/FTC in HIV-uninfected men and men who become HIV-infected while taking PrEP needs evaluation [112-114]. The PROUD clinical trial in the UK and the IPERGAY clinical trial in France and Canada report that PrEP is highly protective against HIV acquisition among HIV-negative MSM and that PrEP use was not associated with increased number of sexual partners, decreased condom use, or increased incidence of STIs [115,116]. PROUD and IPERGAY data were not available when this review was performed but should be taken into account when providing guidance on PrEP.

In Europe, structural barriers including human rights violations, homophobia, direct and indirect discrimination and obstructive policies and laws all limit the

effectiveness of HIV intervention programmes, by reducing service uptake and by compromising the quality of services. In the European Survey of Lesbian, Gay, Bisexual and Transgender persons conducted in 2012, 38% of European MSM respondents said that they were not open with any healthcare provider about their sexual orientation; the percentage of men saying this was 70% or higher in several EU countries, including Lithuania, Slovakia, Romania, Poland, and Latvia [117]. Structural interventions aiming to decrease stigma and discrimination against MSM could result in an open climate where MSM feel safe to disclose their sexual practice and enrol in prevention and treatment programmes. Evaluation research is needed to guide how structural interventions for MSM in Europe would best be designed and implemented. As LGBTI rights improve in diverse European settings there will be opportunities for evaluating the health impacts that might be achieved due to structural and policy changes, and these should not be missed.

More descriptive data are needed on morbidity, wellbeing and health service use among MSM and MSM sub-populations. To minimise selection bias inherent in sampling strategies such as purposive or voluntary recruitment, combinations of sampling strategies that complement each other may increase validity. These may include the inclusion of sexual identity and practice variables in service monitoring, respondent driven sampling in real-life or on the web and time-location sampling.

This systematic review of HIV prevention interventions among MSM aimed for a comprehensive evidence-based multidisciplinary approach. The HASTE grading framework that is designed to evaluate HIV interventions among MSM allowed for an inclusive approach employing three tiers of data, and was particularly helpful for highlighting the importance of implementation data. In the grading process, we spent time thoroughly discussing the differences between HASTE grade 2a probable, 2b possible and 2c pending for recommendation. These grades overlap somewhat, and careful consideration is required when assigning them.

Behavioural and biological outcomes were assigned the same value according to the inclusion criteria for this review. As HIV incidence studies are rare, this review argues that all available efficacy data are relevant to include if the specific outcome variables are transparently reported. Reliance on self-reports of sexual risk behaviour is however subject to recall bias and social desirability bias, which may have diluted the measured effects of some interventions [118]. Most studies applied a short recall duration, which has been shown to maximise self-report accuracy and thereby diminish recall bias [119].

In this review it was notable that studies usually evaluated a mix of different (often related or entangled) interventions rather than a single component intervention. Similarly, outcome data in intervention studies are usually combined without disaggregating results by, for example, knowledge of partners' HIV status. Hence the effects of different individual components as well as effects in MSM sub-groups might be diluted in some results.

Serosorting was assigned an insufficient grade of recommendation and is not to be considered as a HIV intervention that should be recommended for MSM. However, many MSM in Europe use this tactic and so communication around serosorting, including the risk of HIV transmission and acquisition as well as STI acquisition, is important to address in counselling and information to MSM.

Encouragingly, fifteen interventions were graded to be strongly, probably or possibly recommended. These interventions can complement each other to maximise their impact and to address prevention needs and preferences of a diverse population of MSM. Offering and implementing prevention packages in collaboration with community members is crucial to the success of national and sub-national prevention programmes in the EU/EEA. In the relatively resource-rich European setting, there is an opportunity to provide global leadership with regard to the regional scale-up of comprehensive effective HIV prevention interventions for MSM.

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Conflict of interest

Authors report no conflict of interest.

Authors' contributions

SS prepared the manuscript and managed revisions. MS and SS carried out the data collection. AT led the study team. All authors participated in the study design, the interpretation of data and revised the manuscript for intellectual content. All authors approved the final manuscript.

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