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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].

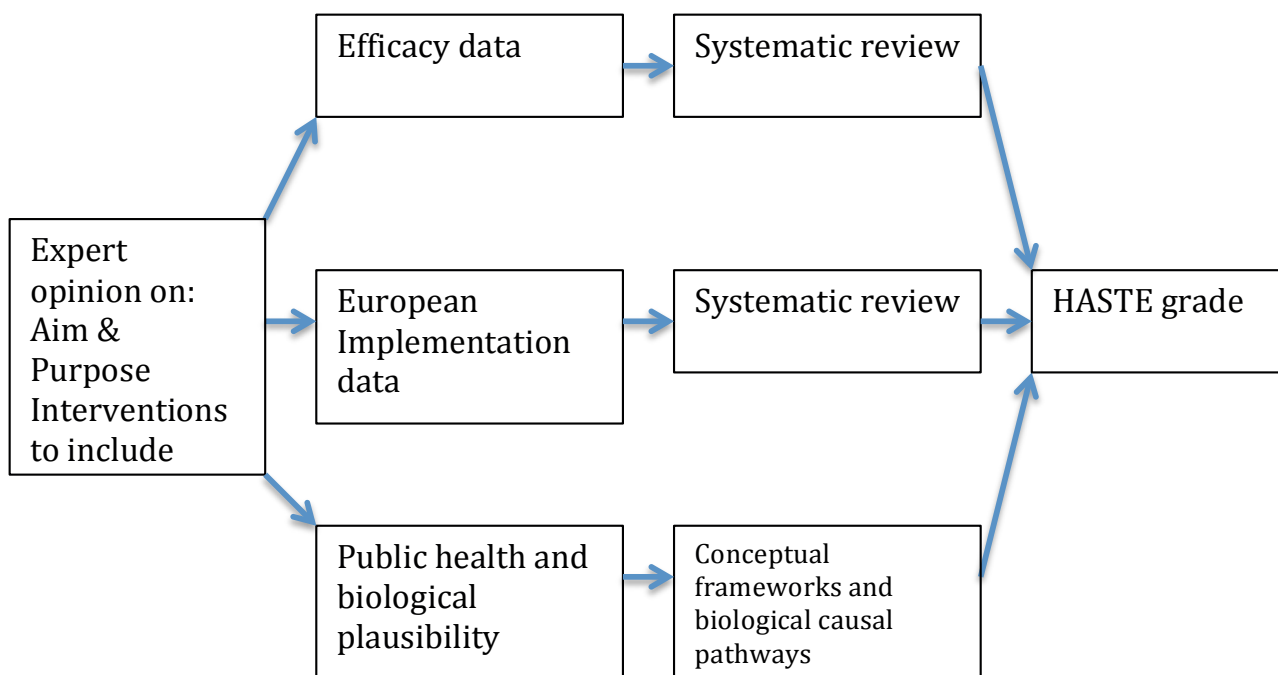
The objectives of this review were to identify and describe studies evaluating the efficacy, and effectiveness of HIV prevention interventions among MSM in relation to implementation data from the European setting, and to further appraise the evidence according to the Highest Attainable Standard of Evidence (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 1Highest Attainable Standard of Evidence (HASTE) system for HIV interventions^a

Grade level		Strength of recommendation	Explanation
Grade 1		Strong	<ul style="list-style-type: none"> • High plausibility • Efficacy is consistent • Large body of consistent implementation data
Grade 2	Grade 2a	Conditional: probable	<ul style="list-style-type: none"> • Plausibility • Limited efficacy data • Consistently effective from implementation data
	Grade 2b	Conditional: possible	<ul style="list-style-type: none"> • Plausibility • Limited or inconsistent efficacy data • Limited or paucity of implementation data^b
	Grade 2c	Conditional: pending	<ul style="list-style-type: none"> • Plausibility • Ongoing efficacy trials
Grade 3		Insufficient	<ul style="list-style-type: none"> • Undefined plausibility • Inconsistent data • Inconsistent or paucity of implementation data
Grade 4		Inappropriate	<ul style="list-style-type: none"> • 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 plausibility	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 plausibility	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 plausibility	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 plausibility	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 plausibility	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

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 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 plausibility	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 where 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 sero-conversion [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 to 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, well-being 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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