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Successes and challenges of HIV prevention in men who have sex with men

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This is the third in a Series of six papers about HIV in men who have sex with men

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See Online for appendix

Men who have sex with men (MSM) have been substantially affected by HIV epidemics worldwide. Epidemics in MSM are re-emerging in many high-income countries and gaining greater recognition in many low-income and middle-income countries. Better HIV prevention strategies are urgently needed. Our review of HIV prevention strategies for MSM identified several important themes. At the beginning of the epidemic, stand-alone behavioural interventions mostly aimed to reduce unprotected anal intercourse, which, although somewhat efficacious, did not reduce HIV transmission. Biomedical prevention strategies reduce the incidence of HIV infection. Delivery of barrier and biomedical interventions with coordinated behavioural and structural strategies could optimise the effectiveness of prevention. Modelling suggests that, with sufficient coverage, available interventions are sufficient to avert at least a quarter of new HIV infections in MSM in diverse countries. Scale-up of HIV prevention programmes for MSM is difficult because of homophobia and bias, suboptimum access to HIV testing and care, and financial constraints.

Introduction

Men who have sex with men (MSM) have always had a key role in the global HIV epidemic.¹ HIV epidemics in MSM are re-emerging in high-income countries² and have been noted in many low-income and middle-income countries.^{3,4} We review HIV prevention interventions for MSM, emphasise the importance of the development and assessment of combination prevention packages, and address challenges. The World Bank used the highest attainable standard of evidence (HASTE) system (which also includes data for implementation science) in its 2011 review⁵ of published work, whereas WHO used the grading of recommendations assessment, development and evaluation (GRADE) system.⁶ We combine these reviews and our own comprehensive review of work and suggest a conceptual framework for packaging of interventions and modelling of the potential effect of scale-up of HIV prevention interventions for MSM.

Search strategy and selection criteria

Between Oct 11, 2011, and Jan 9, 2012, we reviewed HIV prevention interventions for MSM published in English on PubMed, Embase, Scopus, PsycINFO, Social Sciences Citation Index, Science Citation Index Expanded, Conference Proceedings Citation Index–Science, and the Cumulative Index to Nursing and Allied Health Literature, and focused whenever possible on systematic reviews and meta-analyses (appendix). We also inventoried the results of meta-analyses of HIV prevention in MSM. We compiled 1871 non-duplicated citations and refined our results to identify 60 articles with putative HIV prevention interventions tested in MSM. Further details of our search strategy and bibliographies for all included articles, systematic reviews, and meta-analyses are in the appendix.

Key messages

- Governmental, academic, and community strategies have been insufficient to curb the HIV epidemic in men who have sex with men (MSM).
- HIV prevention is difficult for MSM because of the high biological risk associated with anal intercourse, high frequency and variety of sexual activity, little acknowledgment of male–male sex by governments and health-care providers, discrimination, few specific services for MSM, and syndemic challenges (eg, substance misuse).
- In most parts of the world, restricted resources and legal barriers complicate the effective provision of HIV prevention services for MSM.
- Resources are scarce for HIV prevention services in MSM and scale-up is problematic. Available interventions are insufficient, largely untested in most developing countries, and not sufficiently tailored to MSM.
- Several behavioural interventions are somewhat efficacious in reduction of the frequency of unprotected anal intercourse in MSM, but none effectively decreases the incidence of new HIV infections. However, behavioural interventions have not been fully assessed in some environments, and they have a crucial role in combination with barrier and biomedical interventions.
- Coordinated behavioural, biomedical, and structural interventions that incorporate efficacious strategies could substantially reduce the incidence of HIV infection in MSM.
- Prevention efforts reach only a small proportion of MSM, and scalability should be considered when new interventions and packaging approaches are developed.

Prevention interventions

Early HIV prevention efforts focused on behaviour change and yielded many successes, but did not provide sufficient strategies to curb the epidemic. More recently, approaches have been inclusive of biomedical strategies. Treatment and behavioural and biomedical approaches are not at odds with one another, but rather have complementary roles in a broad, coordinated, and science-based approach to HIV prevention in MSM. Indeed, the strengths and opportunities associated with each strategy suggest that the intelligent combination of approaches is better than any single approach.

We comprehensively reviewed studies of HIV prevention in MSM (figure 1). Table 1 shows broad categories of HIV prevention approaches for MSM and evidence for their effects. We noted important gaps in the evidence base for HIV prevention in MSM. Even when MSM were represented in studies, they were often not the focus of the investigation. Behavioural interventions have the strongest evidence but have only slight effects on self-reported behaviours, and no evidence shows a reduction in the incidence of HIV infection. Barrier and biomedical interventions have higher estimated efficacy (including for reduction of the incidence of HIV infection) than do behavioural interventions, but this efficacy might not be supported by evidence from randomised trials (eg, condoms) or have been tested in many MSM—eg, treatment as prevention. Other approaches—such as testing for and treatment of HIV and other sexually transmitted infections (STIs)—have strong biological plausibility and collateral prevention benefits but do not effectively lessen the incidence of HIV infection.

Behavioural interventions

Stand-alone behavioural interventions are not sufficient to reduce HIV transmission in MSM.⁷ Previously, behavioural interventions typically targeted sexual risks such as unprotected anal intercourse and having many sex partners, substance or alcohol use, and adherence to antiretrovirals. Such interventions seem to decrease the frequency of unprotected sex by about 27% compared with control populations exposed to few or no HIV prevention interventions, and by 17% compared with controls administered standard HIV prevention interventions (usually testing and counselling).⁸ However, behavioural interventions have important limitations. Efficacy is generally slight, fidelity is of concern, and few resources are available to bring individual or multisession (ie, those in which more than one contact is necessary) approaches to scale. Furthermore, most randomised studies have been done in North America or Europe (appendix), where most substantial investment has been made in the scale-up of behavioural interventions. However, even in these areas, biomedical approaches are increasingly emphasised.

The HIVNET 015 study (colloquially called EXPLORE)—one of the few studies of behavioural interventions in

MSM for which reduction of the incidence of HIV infection was an endpoint—clearly shows the potential and limitations of behavioural approaches.⁹ It was a randomised study of more than 4000 US MSM in six cities comparing biannual HIV testing and risk-reduction counselling with individualised intensive risk-reduction counselling. Investigators reported significant falls in the frequency of unprotected receptive anal intercourse in the intensive counselling group. However, the incidence of HIV infection in the intensive counselling group was not significantly lower than that in the control group. Results of post-hoc analysis of data from intermediate timepoints suggested significant but transient reductions in the incidence of HIV infection, and emphasised the need for long-term assessments of behavioural interventions. Retention was lower in the intervention than in the control group, suggesting that intensive, multisession interventions might not be universally acceptable. Additionally, self-reported falls in the frequency of risky behaviours are an insufficient standard for measuring the efficacy of interventions to prevent HIV acquisition.

Few rigorous assessments of theory-based behavioural interventions are available in developing countries (appendix). Behavioural interventions might be more effective in settings that have little experience of specific prevention interventions and programmes for MSM than in those which have a lot of experience of such

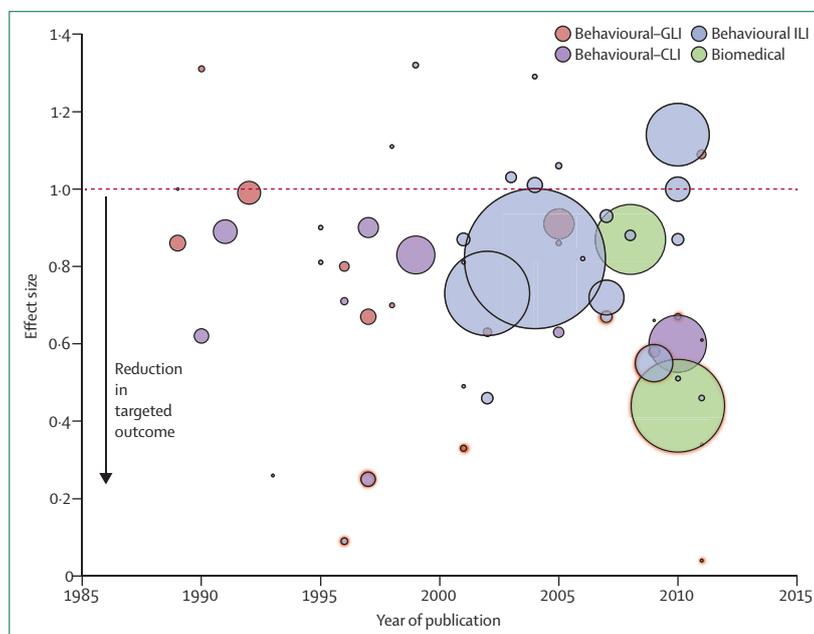


Figure 1: Effects of HIV prevention interventions for MSM, by number of MSM included in study, significance, and intervention type

Effect size is expressed as a risk ratio when possible, but in some cases represents an odds ratio or prevalence ratio. Outcome was unprotected anal intercourse in 54 cases, HIV or other sexually transmitted infection in five, and number of sex partners in one. Red halos show significance. The red dotted line signifies a null effect (ie, no increase or decrease in the targeted outcome). The appendix contains further information and references for included interventions. MSM=men who have sex with men. GLI=group-level intervention. ILI=individual-level intervention. CLI=community-level intervention.

	Unprotected anal intercourse			HIV incidence			HASTE grade
	Effect	Evidence	Efficacy	Effect	Evidence	Efficacy	
Individual-level interventions addressing HIV risk	↓	A	7%*	None	A	None	2a
Group-level interventions addressing HIV risk	↓	A	29%*	Not separately rated
Network-based or peer-based interventions addressing HIV risk	↓	A	25%*	1
Condom use	↓	C	78%†	1
Diagnosis and treatment of herpes simplex virus type 2	None	B	None	4
Circumcision	None	C	None	2b
Pre-exposure prophylaxis	↓	B	44%	2a
Postexposure prophylaxis	↓	D	81%‡	2a
Antiretrovirals as prevention	↓	B	96%§	1
Testing for HIV and informing people of positive serostatus	↓	C	68%*	1
Condom availability and distribution	↓	A	45%	1

HASTE criteria comparisons are reproduced from Baral et al.⁵ ↓=outcome is decreased by intervention. A=consistent conclusions across meta-analyses, high-quality systematic reviews, or several randomised controlled trials. B=evidence from one or two randomised controlled trials. C=high-quality systematic reviews with some inconsistent conclusions, or several consistent ecological or cohort studies. D=cross-sectional association, case series suggesting outcome, or single cohort study. HASTE grades: 1=strong; 2a=probable; 2b=possible; 3=insufficient; 4=inappropriate. MSM=men who have sex with men. HASTE=highest attainable standard of evidence. iPrEX=pre-exposure prophylaxis initiative. *From meta-analysis. †From a large observational study cohort of MSM. ‡From case series data for percutaneous exposure for single-drug therapy. §From a cohort of mainly heterosexual couples from a randomised study of early treatment.

Table 1: Categories of HIV prevention interventions for MSM and effects on frequency of unprotected anal intercourse and incidence of HIV infection

strategies. Research is needed to assess the acceptability and cultural relevance of such approaches in these settings. If interventions have little cultural relevance, then adaptation or full re-evaluation might be necessary.

If behaviour change is achieved to an adequate scale, transmission of HIV can be reduced. The responses of gay communities in the USA, Canada, and Australia^{10–13} to the AIDS epidemic in the 1980s show that community-initiated strategies can have an important role in shaping of epidemics. After the discovery of the viral cause of AIDS and the development of an antibody test, MSM in several countries^{10–13} reduced their numbers of sex partners and used condoms more often than before, and the incidence of HIV infection fell sharply in some settings.¹⁴ More recently, seroadaptive strategies such as serosorting and strategic positioning have arisen in communities of MSM, and have been assessed in partnership with public health and academic researchers.

Researchers have assessed the efficacy of interventions to increase adherence to antiretroviral therapy.¹⁵ Because of the preventive value of suppression of HIV viral load, these interventions should have added importance in the future. Proven interventions to increase adherence to antiretrovirals¹⁶ could serve as a basis for development of adherence strategies targeted at HIV-negative men prescribed oral pre-exposure prophylaxis. Much evidence shows that alcohol and use of non-injection drugs are important drivers of HIV infections in MSM communities worldwide.^{17,18} Thus, behavioural or drug interventions that decrease alcohol consumption¹⁹ and the use of stimulants such as metamfetamine²⁰ might be important adjunctive approaches in MSM and could lead to a fall in HIV transmission.

Biomedical and barrier interventions

Biomedical and barrier approaches destroy HIV in the rectal or vaginal compartment, create a hostile environment (which can be pharmacological or immunological) that prevents local viral replication, or provide a barrier between the virus and susceptible cells. Evidence shows that condoms and pre-exposure treatment with antiretrovirals reduce the risk of HIV infection. The efficacy of other approaches—eg, postexposure treatment with antiretrovirals, HIV vaccines, use of antiretrovirals for prevention—is supported by evidence in non-MSM populations. Strategies such as treatment of drug addiction and STIs are probably important but empirical evidence is weaker for them than for other interventions. Additionally, injection-drug-using MSM should have access to proven biomedical prevention strategies such as needle exchange and opioid-substitution treatment, especially in regions of the world where injection drug use is a major driver of the HIV epidemic.²¹

Condoms

Condoms are highly efficacious in HIV prevention. A Cochrane review²² showed that use of condoms reduced HIV transmission in HIV-discordant heterosexual couples by an estimated 85%. Investigators of the collaborative HIV seroincidence study²³ suggested that for receptive anal intercourse, condom use reduced the per-contact risk of HIV infection by 78% compared with unprotected anal intercourse. Despite these findings, condom use by MSM is problematic. Issues include difficulty in negotiating condom use with sexual partners,²⁴ condom slippage or breakage,²⁵ and availability in developing countries.²⁶ The Reality female condom has been assessed for safety and acceptability for anal sex in MSM. However, participants reported condom

slippage, pain, and rectal bleeding.²⁷ The female condom has been redesigned; tolerability in anal intercourse for MSM is unknown, but should be explored.

Condom-compatible lubricants probably provide additional prevention benefits (when used with condoms) because they reduce condom breakage and rectal trauma.²⁵ Furthermore, men without access to water-based lubricants might use petroleum jelly, body cream, or saliva,²⁸ increasing the risk of condom failure and transmission of viral infections.¹⁸ Regular use of lubricant without condoms has been associated with an increased risk of STIs,²⁹ and the use of hyperosmolar formulations might increase risk for HIV infection.³⁰

Antiretrovirals

Antiretroviral therapy can be given to HIV-negative people after a high-risk HIV exposure (so-called post-exposure prophylaxis; appendix) or before potential high-risk activity (pre-exposure prophylaxis). The pre-exposure prophylaxis initiative (iPrEx) was a study³¹ designed to assess the safety and efficacy of pre-exposure prophylaxis with daily tenofovir and emtricitabine (Truvada) in MSM and transgender women. 2499 HIV-negative men and transgender women were followed up for a median of 1.2 years. Participants receiving tenofovir and emtricitabine had a 44% reduction in the frequency of HIV infections compared with those given placebo. The regimen was fairly well tolerated, but researchers noted a transient but significant increase in nausea and unintentional weight loss in the tenofovir and emtricitabine group. Self-reported compliance was high ($\geq 89\%$ at week 4), but drug concentrations in participants suggested that actual adherence was probably lower. Adherence was low in some sites outside the USA. A Consensus Committee of the Southern African HIV Clinicians Society³² has published guidelines on the use of pre-exposure prophylaxis in MSM deemed at high risk for HIV acquisition. These guidelines recommend daily tenofovir and emtricitabine and HIV antibody tests every 2–3 months.³²

The iPrEx study is a milestone in HIV prevention research, and is notable both for its results and the inclusion of MSM from low-income and middle-income countries such as South Africa, Thailand, Peru, and Ecuador. However, its findings also raise issues that have to be resolved before oral pre-exposure prophylaxis can be fully integrated into HIV prevention strategies. The potential for long-term toxic effects should be established, as should acceptability,³³ training procedures for prescribers, methods to avoid failing to diagnose occult infections during the window period, how to monitor adverse events, whether viral resistance will be problematic, and whether intermittent dosing regimens will be as efficacious as daily dosing. Additional research should focus on which subgroups of MSM should receive oral pre-exposure prophylaxis and for how long, and how to fund this intervention.

Results from HPTN-052 showed that treatment of the infected partner in a group of (mostly heterosexual) HIV-serodiscordant couples could reduce transmission to the uninfected partner by 96%.³⁴ The implications of this finding for HIV prevention in MSM are not immediately clear. Very few same-sex couples were included in the study, and a separate analysis of efficacy in MSM was not possible. Observational studies suggesting that treatment of HIV-positive people is effective for HIV prevention have been reported in heterosexual populations,³⁵ but a systematic review identified no studies focusing on MSM.³⁶

Community interventions

At a community level, programmes to promote comprehensive HIV testing, linkage to care, and viral suppression through treatment with antiretrovirals are proposed by prevention scientists to lower the viral load and thereby decrease transmission of HIV. In San Francisco, where most HIV infections occur in MSM, early ecological analyses³⁷ suggest that decreases in community viral load are associated with a fall in the incidence of HIV infection. However, the period of observation in San Francisco coincided with changes in surveillance practice. Reports from Australia³⁸ describing ecological patterns in HIV infections after the introduction of antiretroviral therapy did not show similar effects. Powers and colleagues³⁹ estimated that patients with early infection (ie, within 6 months of initial infection) have a crucial role in heterosexual epidemics and account for as much as 39% of new HIV-1 transmission. Phylogenetic data suggest that 27% of incident HIV infections in MSM in London, UK were from partners recently infected with HIV.⁴⁰ If this finding is true, the role of treatment as prevention might be less important for MSM than for heterosexuals.

Despite these uncertainties, treatment of HIV-positive MSM to reduce HIV transmission has biological plausibility³⁴ and is congruent with clinical benefits for men who start HIV treatment early.⁴¹ Furthermore, provision of treatment for HIV infection as prevention builds on an established clinical infrastructure and thus is arguably better prepared for scale-up of service provision than is the infrastructure for provision of oral pre-exposure prophylaxis to HIV-negative men. As prevention strategies based on antiretroviral treatment or prophylaxis are implemented, behavioural and clinical surveillance systems will be important to monitor risk compensation.⁴² The benefits of proven risk-reduction interventions could be mitigated if people increase their risk behaviours because of perceived protection.

Microbicides

When applied to the vaginal or rectal mucosae, microbicides prevent or substantially reduce the acquisition of HIV or other STIs.⁴³ The results of the Centre for the AIDS Programme of Research in South Africa

(CAPRISA) 004 study⁴⁴ showed that a vaginal microbicide gel containing 1% weight/weight tenofovir reduced HIV acquisition in women by 39% compared with placebo.⁴⁴ The same gel provided substantial protection against rectal challenge in non-human-primate studies,⁴⁵ providing a rationale for the development of a rectal microbicide containing tenofovir. Some MSM have expressed interest in the use of this type of product.^{46,47} The investigators of a phase 1 rectal safety study⁴⁸ of 1% tenofovir vaginal gel (RMP-02/MTN-006) noted that rectal administration results in extremely high tenofovir concentrations to rectal tissue and can prevent HIV infection in an ex-vivo–in-vitro challenge model of HIV infection.⁴⁸ However, the vaginal gel had to be reformulated for HIV treatment because of low tolerability.⁴⁸ Another phase 1 study⁴⁹ (MTN-007) explored the rectal use of a reduced glycerin formulation of tenofovir 1% gel. This formulation seems to be safe and well tolerated.⁴⁹ Phase 2 assessments of the reformulated gel will be done in MSM and transgender women in the USA, Thailand, South Africa, and Peru and are expected to begin in 2012.⁵⁰

Vaccination

Two trials of HIV vaccine efficacy are of particular relevance to MSM. In the Step study⁵¹ (HVTN 502/Merck 023), the replication-incompetent adenovirus 5 vector might have increased the risk of HIV infection in uncircumcised MSM with pre-existing neutralising antibodies specific to the adenovirus. The results of the Thai RV144 trial⁵² showed a significant (31%) reduction in HIV acquisition in people given the vaccine compared with those given placebo.⁵² However, the heterosexual men in this trial were at low risk for HIV infection, and the high risk of transmission associated with anal sex could be more difficult to prevent with a vaccine. A trial that would allow an appropriately powered analysis of this issue has been proposed in Thai MSM. Workers in non-human-primate research now use rectal challenges—a key advance in the development of vaccines that protect against infections through the gut mucosa.

The potential synergy between vaccines and pre-exposure prophylaxis is of interest. Pre-exposure prophylaxis might protect individuals from HIV infection while allowing induction of host protective responses from vaccination and HIV exposures.⁵³ This finding has been noted in non-human primates⁵⁴ and warrants further study in clinical trials.

HIV testing

HIV testing underlies the effectiveness and implementation of nearly all other prevention approaches and is the gateway to the offering of services tailored to client needs. HIV testing itself is an intervention; meta-analytic evidence shows that most people who discover that they are HIV positive take steps to reduce the risk of

transmission to others.⁵⁵ Furthermore, many MSM are unaware of their HIV serostatus.^{56,57} Accurate knowledge of serostatus is probably a key driver of whether community-adopted prevention strategies—eg, serosorting—confer protection or increase the risk of HIV transmission and acquisition (appendix).

Diagnosis and treatment of STIs

Bacterial and viral STIs can increase the efficiency of HIV transmission.^{58,59} Urethritis increases seminal viral load in HIV-positive MSM,⁶⁰ and increased virus numbers in semen are associated with high transmission risk in heterosexual men.⁶¹ However, to show that syndromic treatment of STIs with antibiotics prevents HIV acquisition is difficult.⁶² High-quality evidence suggests that suppression of herpes simplex virus type 2 in MSM does not prevent HIV transmission.^{63,64} Incident STIs are a clear marker of history of sexual risk and are predictive of future acquisition of HIV infection;⁶⁵ thus diagnosis of STIs in MSM offers opportunities to identify high-risk men for prevention services. Treatment of STIs has inherent benefits for men's health, offers opportunities for discussion of sexual risks and strategies for risk reductions, and is predicted to reduce the infectiousness of HIV-positive men.

Combination prevention

Any single prevention modality is unlikely to provide complete protection from HIV infection.⁶⁶ Combination of treatment interventions to produce a synergistic effect is not new,⁶⁷ and multilevel HIV prevention has been advocated in a previous *Lancet* Series.⁷ Prevention packages are combinations of HIV prevention interventions, assembled to work together to optimise effectiveness. Several principles should guide the development and testing of such prevention packages. Prevention packages might be most likely to succeed if they target several points in the pathway to HIV infection, address major drivers of HIV epidemics with efficacious primary interventions, improve the effectiveness of these interventions through combination, and provide basic strategies that support prevention and respect ethical imperatives for MSM.

Partner selection that results in HIV-discordant sexual dyads, anal sex, HIV RNA concentrations in HIV-positive sex partners, and an absence of condom use for anal sex could be important targets for intervention. Environmental factors such as availability of condoms and condom-compatible lubricant, societal policies and prejudices that promote or discourage stable sexual partnerships,² and access to culturally competent health-care services can affect the extent to which prevention targets are affected so as to promote or deter HIV transmission. Ideally, combination HIV prevention packages will address several targets for intervention with behavioural, biomedical, and structural approaches.

The main targets for intervention packages should be important drivers of epidemics for which maximally efficacious interventions are available. Risk of HIV transmission in MSM is noteworthy because of the very high per-act risk of transmission from anal intercourse.⁶⁸ Reduction of the time-density of increased viral load decreases HIV transmission in discordant heterosexual couples with 96% efficacy.⁶⁹ Thus, interventions to lessen the frequency of unprotected anal intercourse in HIV-discordant partnerships and reduce the HIV RNA concentrations of HIV-positive MSM should be priority targets in prevention packages. The strongest evidence for efficacy in prevention of sexual transmission of HIV infection is associated with barrier and biomedical interventions, such as consistent and correct condom use (which reduce transmission by 78–85%),^{22,23} early provision of antiretroviral therapy to HIV-positive sex partners in discordant heterosexual couples (96%),^{69,70} and provision of pre-exposure prophylaxis in high-risk HIV-negative MSM (44–73%, depending on adherence).⁷¹

Coordinated behavioural interventions are important to enhance the effectiveness of primary biomedical prevention approaches. Multisession interventions slightly reduce the frequency of unprotected anal intercourse.^{9,72} Behavioural interventions that promote adherence to antiretroviral therapy⁷³ might be important to maximise effectiveness. Behavioural approaches could also be important in reduction of risk compensation in the context of oral pre-exposure prophylaxis or future vaccines and microbicides.

Knowledge of HIV status is crucial for decision making about condom use and early access to antiretroviral therapy. Interventions that provide knowledge about how HIV is transmitted are important for promotion of condom use. The results of a meta-analysis⁷⁴ show that free condom distribution programmes increase condom use in non-MSM populations. Promotion of knowledge about HIV serostatus and how the virus is transmitted has an ethical and rights-based rationale, as does the

availability of basic prevention supplies to reduce the risk of HIV transmission through sex.⁷⁵ On the basis of these considerations, we present a conceptual framework for packaging of prevention interventions for MSM and provide sample components in table 2. Table 3 shows specific examples of combinations of proven biomedical interventions with adjunctive behavioural and related structural interventions.

Clinical trials of packaged interventions are a challenging but necessary step in the development of a rational approach to prevention of HIV infection in MSM.^{76–78} Specific methodological challenges include the absence of a reliable assay of the incidence of HIV infection, naive control groups, and surrogate markers to assess efficacy, and the poor reliability of self-reported risk to predict reductions in incidence.⁹ Trials will probably be costly, and how best to balance resource needs for these studies with financial requirements for simultaneous provision of basic prevention resources is an important scientific and ethical issue.⁷⁵ Studies developing and testing the feasibility of HIV prevention packages for MSM are ongoing in the Americas, Africa, and China (appendix).

Modelling

To establish the potential effect of intervention packages at a population level, we used the stochastic, agent-based simulation model of HIV transmission that was developed for the Prevention Umbrella for MSM in the Americas Project, and used by Beyrer and colleagues (their appendix describes the modelling framework in detail).⁶⁸ We used a more fully parameterised model to represent the MSM transmission network for four case studies of epidemic patterns: an MSM-focused epidemic in a developed country (USA), an MSM-focused epidemic in a developing country (Peru), a widespread epidemic mainly in heterosexual people with some transmission in MSM (Kenya), and a mixed epidemic in heterosexuals, MSM, and injecting drug users (India). Details of this parameterisation, including data sources and selected

	Biomedical interventions	Behavioural interventions	Structural enablers
High biological risk of acquisition of HIV infection after unprotected anal intercourse	Condoms; condom-compatible lubricant; pre-exposure prophylaxis	Increase condom use and adherence to pre-exposure prophylaxis; reduce alcohol and drug use	Availability of condoms and condom-compatible lubricant; culturally competent health care; rational policy to support biomedical and behavioural strategies to reduce drug and alcohol use
High viral load in HIV-positive partners	Antiretrovirals for HIV-positive men	Increase adherence to antiretrovirals	Culturally competent health care; stable supply chains for antiretrovirals; capacity for laboratory monitoring
High frequency of STIs	Screening for and treatment of STIs	Support and reminders for routine screening for STIs	Culturally competent health care; training of health-care providers to ensure appropriate screening sites for STIs and adequate testing frequency
High prevalence of HIV infection in partners of HIV-negative men; low awareness of HIV serostatus	Testing for HIV	Support and reminders for routine screening for HIV infection in HIV-negative MSM; increase disclosure of HIV status; encourage reduction of numbers of sexual partners	Culturally competent health care; removal of legal or structural barriers that prevent frequent screening; structural disclosure approaches (eg, couples counselling and testing)

MSM=men who have sex with men. STIs=sexually transmitted infections.

Table 2: Key drivers of HIV epidemics in MSM and related biomedical and behavioural interventions

	Barrier and biomedical components	Behavioural components	Structural components
Condoms	Condoms and condom-compatible lubricant	Promotion of routine screening for HIV infection and consistent and correct condom use	Condom distribution programmes; increasing condom availability at locations where people have sex
Treatment as prevention	Early provision of antiretroviral therapy to HIV-positive partners	Promotion of routine screening for HIV infection, linkage to care, and antiretroviral adherence	Provision of culturally competent screening and care services; promotion of safe spaces for HIV testing for MSM
Pre-exposure prophylaxis	Pre-exposure prophylaxis for high-risk HIV-negative MSM	Promotion of routine screening for HIV infection, reduction of partner numbers, and adherence	Provision of culturally competent screening and safe spaces for ongoing monitoring for HIV infection and toxic effects

MSM=men who have sex with men.

Table 3: Candidate HIV prevention packages for MSM, by intervention type

parameter values for the US and Peru are in Beyrer's paper's appendix⁶⁸ and for India and Kenya in our appendix. Setting-specific aspects of the model included sexual behaviour with main and casual partners; role versatility (ie, insertive vs receptive vs versatile); patterns of testing and treatment; patterns of ageing, birth, and death; prevalence of circumcision and sex with women (in MSM); and HIV prevalence in women. Viral load trajectories on and off treatment and transmission probabilities by viral load were constant across models. Baseline models assumed 2011 levels of treatment coverage and condom use for anal sex and no use of pre-exposure prophylaxis. Baseline models were calibrated against independent sources of prevalence data (appendix).

We simulated three prevention packages based on condoms, oral pre-exposure prophylaxis, and improved antiretroviral initiation (ie, more people taking antiretrovirals and more prompt initiation of antiretroviral therapy), respectively and applied them to the baseline models. We based uptake, adherence, and response on findings from our systematic review (appendix). If few data were available, we did sensitivity analyses across several variables selected on the basis of expert opinion. To show the need for adequate resources for scale-up, we modelled the effect of prevention at varying levels of intervention coverage. We investigated the idea that packaging of complementary interventions together increases their effect with the oral pre-exposure prophylaxis package model at three levels of adherence and corresponding estimated efficacy to simulate implementation with and without supportive adherence interventions. Although not modelled here, adherence is important for the antiretroviral-therapy-based package. We assessed the effect of each intervention scenario as the proportionate reduction in the number of new infections within 10 years after rollout compared with that at baseline, and the effect of varying degrees of coverage.

The results of our modelling show that, if oral pre-exposure prophylaxis and antiretroviral treatment coverage were assumed to be 40%, and 20% of unprotected anal intercourse encounters were replaced with condom-protected intercourse, between 7–29% of

incident HIV infections would be averted during 10 years (figure 2). Increasing pre-exposure prophylaxis coverage from 20% to 80% increased the estimated cumulative proportions of infections averted (figure 3). Additional data about varying coverage of antiretroviral therapy and condom provision are included in the appendix. Increasing the frequency of pre-exposure prophylaxis adherence sufficient to achieve the high efficacy (ie, a 73% reduction in acquisition of HIV infection) in men from 50% to 75% resulted in higher estimates of averted HIV incidence in all countries compared with baseline. However, the number of infections averted did not rise when we increased the modelled proportion of men with sufficient adherence from 75% to 90% (figure 4).

The results of the modelling show several key notions of HIV prevention for MSM. First, packages of interventions with sufficient coverage can have pronounced effects on the incidence of HIV infection in MSM worldwide. Second, a high degree of coverage for efficacious interventions is important to increase their effect. In many cases, coverage will be poor irrespective of funding until men can safely access care, comfortably discuss their sexual risks for HIV with health-care providers, receive referrals for appropriate services, and confidently use prevention methods and services that will reduce their risks of acquisition or transmission of HIV infection. Finally, packaging of complementary interventions—eg, adherence support—can increase the effect of primary biomedical interventions.

Between-country variations in the proportion of infections averted could be because of stochasticity, differences in underlying baseline conditions, or a combination of both. For example, the proportion of infections averted through use of the antiretroviral therapy package was higher in countries that had less treatment and lower baseline CD4 counts at the beginning of treatment than it was in countries with more treatment and higher CD4 counts. The estimated number of infections averted by the condom package was higher in India than in other countries, which could be partly because of higher estimates of baseline condom use in India.

Scale-up

Even if trials of tailored intervention packages are successful, their scale-up and implementation are uncertain. Availability of basic HIV prevention services for MSM is poor, foreshadowing the challenges of implementation of further complicated and costly packages. However, a global model of successful implementation of multicomponent community health care has emerged in India, where Avahan—the Indian initiative of the Bill & Melinda Gates Foundation—provides behaviour change interventions and related supports to several at-risk populations, as well as treatment for STIs, and clean-needle distribution.⁷⁹

The rise in international aid funding for large global health programmes during the past decade has led to interest in improvement of the science of scale-up. Success factors include choosing of a simple intervention widely thought to be useful, strong leadership and governance, active engagement of various implementers and the target community, tailoring of the scale-up approach to the local situation, and incorporation of research into practice.⁸⁰

The public health infrastructure available to support scale-up of interventions varies greatly between countries and should be considered during planning. For example, government-supported clinics could be primary sites of delivery of services or drugs in some countries. Conversely, countries with deficits of space and trained personnel might find it difficult to bring interventions to scale. Public health surveillance and other strategic information systems will be crucial to assess and monitor outcomes and reach affected communities. Some characteristics of interventions lend themselves to opportunities for scale-up—eg, low cost, fit with existing modes of service delivery, acceptability in MSM and other populations, local adaptability, and easy accurate implementation. When possible, design and planning of new interventions should account for scalability, and funders should favour approaches conducive to scale-up.

Coverage of interventions

To assess coverage of HIV prevention interventions for MSM, identify gaps in provision of core services, and plan resource needs, countries should first establish the coverage of basic prevention services. In many cases, these baseline assessments are not done, or are done inadequately. For example, an assessment of the 2008 UN General Assembly Special Sessions indicators⁸¹ showed that less than 50% of low-income and middle-income countries reported at least one key indicator of provision of prevention services to MSM. A weighted analysis showed that less than a third of MSM globally were tested for HIV infection or reached by any kind of HIV prevention programme.

Coverage of HIV prevention services for MSM is often grossly inadequate, even in some high-income countries. For example, country-specific estimates from

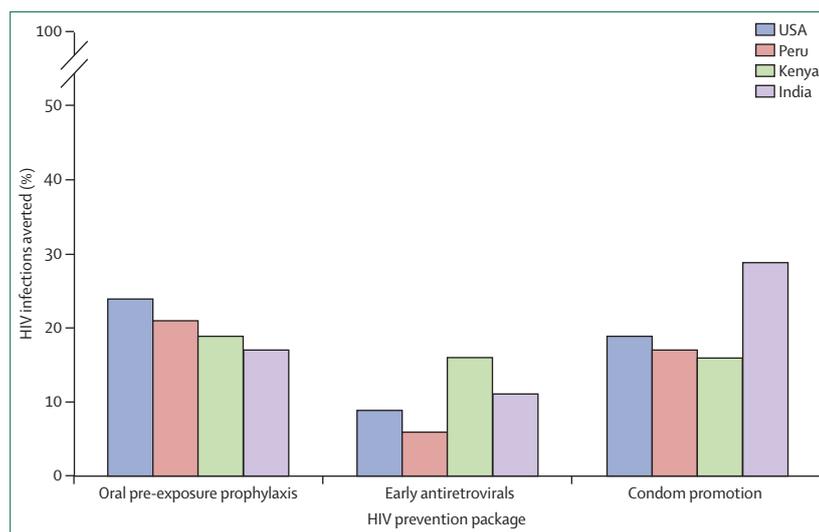


Figure 2: Modelled estimation of proportion of infections averted in 10 years after provision of HIV prevention packages to men who have sex with men

Men were eligible for oral pre-exposure prophylaxis if they were HIV negative and either had unprotected anal intercourse with two or more men in the previous year, or were in an ongoing sexual relationship with a known HIV-positive partner. “Early” means treatment at a CD4 count of 500 cells per μL in the USA and 350 cells per μL in other countries. Coverage is estimated at 40% for oral pre-exposure prophylaxis and early antiretrovirals. A 20% replacement of unprotected anal intercourse with condom-protected intercourse is estimated for the condom package. Bars are the mean of ten simulations.

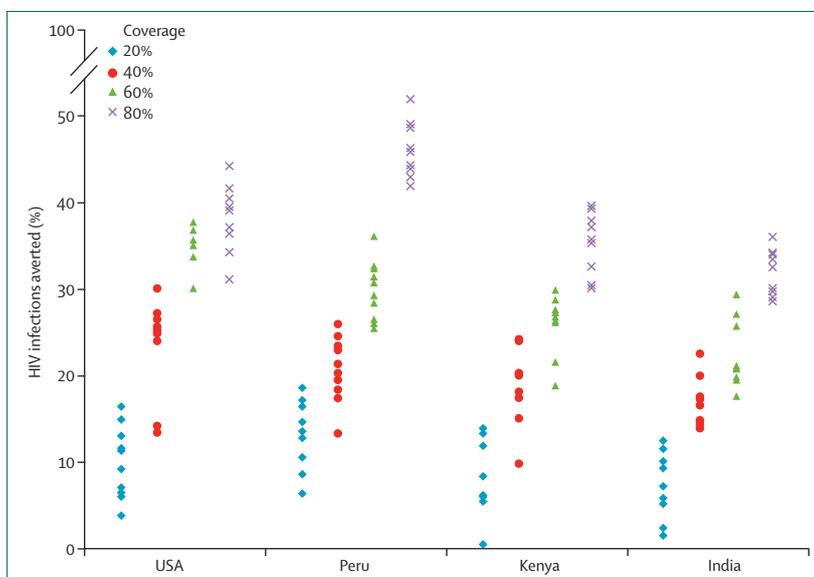


Figure 3: Stochastic simulation estimating the proportion of HIV infections averted in 10 years by an oral pre-exposure prophylaxis prevention package in men who have sex with men, by degree of coverage

Men were eligible for oral pre-exposure prophylaxis if they were HIV negative and either had unprotected anal intercourse with two or more men in the previous year, or were in an ongoing sexual relationship with a known HIV-positive partner. Each symbol is the result of a single simulation; variation is partly because of the size of the simulated population, which is arbitrary. The magnitude of the variation shows the extent of stochastic variation within each scenario, allowing for interpretation of the differences across scenarios and countries.

the 2010 cross-European MSM internet survey⁸² suggest that 25–50% of MSM were tested for HIV infection during the past year, compared with 60% in the Australian periodic gay community survey of MSM,⁸³ and

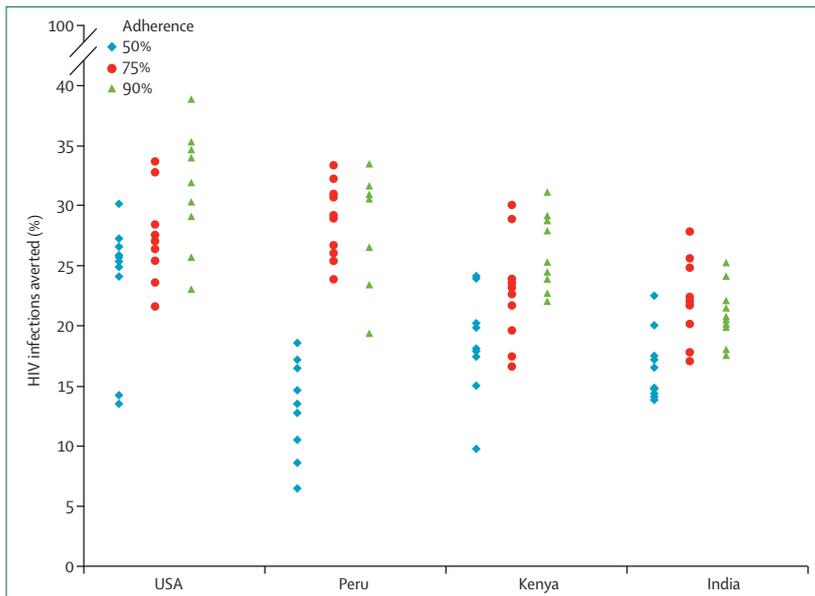


Figure 4: Stochastic simulation estimating the proportion of HIV infections averted in 10 years by an oral pre-exposure prophylaxis prevention package in men who have sex with men with 40% coverage, by degree of adherence

Men were eligible for oral pre-exposure prophylaxis if they were HIV negative and either had unprotected anal intercourse with two or more men in the previous year, or were in an ongoing sexual relationship with a known HIV-positive partner. Each symbol is a single simulation; variation is partly because of the size of the simulated population, which is arbitrary. The magnitude of the variation shows the extent of stochastic variation within each scenario, allowing for interpretation of the differences across scenarios and countries.

77% in the US Centers for Disease Control and Prevention's national HIV behavioral surveillance.⁸⁴ The US report also showed that only 15% of venue-attending MSM (ie, locations where MSM congregate) had received an individual-level and 8% a group-level intervention in the previous year.⁸⁴

New technologies

New technologies offer new opportunities for interventions and to improve efficiency of scale-up for existing interventions. A meta-analysis by Noar and colleagues⁸⁵ showed that, irrespective of the risk population, the efficacy of computer-delivered interventions might be similar to that of human-administered interventions. Technology-assisted interventions might assist with scale-up through provision of efficient ways to administer intervention content and periodic reminders for rescreening, by helping people to find testing centres, and by reaching audiences who might have little access to traditional prevention services, such as rural and non-gay-identified MSM (appendix).

In high-income countries, intervention components can be delivered by high-speed or mobile internet. In low-income and middle-income countries, text messaging applications might be more feasible because technology investments have been more directed towards cell tower infrastructure than towards high-speed internet. Mobile phone ownership is common—eg, South Africa has more active mobile phones than people,

and in Africa overall market penetration is more than 30%⁸⁶—and thus mobile phone interventions have promise in these settings.

Challenging settings

Scarce resources, prevalent prejudice against MSM, criminalisation (of male–male sex, HIV transmission, or sex work), little recognition or nascent organisation of MSM communities, and an absence of cultural competency training for health-care providers can complicate effective HIV prevention programmes for MSM. Prisons are also a challenging setting (appendix). Although all countries struggle with these challenges, many countries in Africa and Asia have difficulties with several of these factors. In Africa and Asia, prevention responses in MSM have been notably absent, or have started but have insufficient coverage (appendix).⁸¹ The first study⁸⁷ in Africa to assess risks for HIV and STIs in MSM was done more than 20 years after the recognition of the virus there.

Prejudice, threats, and violence against people thought to be MSM subvert HIV prevention, care, and treatment in several ways. First, men who do not disclose that they have had male sex partners to their health-care providers are less likely to receive recommended health services than are those who make such disclosure.⁸⁸ If men fear or experience denial of care when they disclose male sex partners, they will be less likely to present their risks to health-care providers than if they are assured of being offered care, irrespective of sexuality.¹⁸ Men might be reluctant to use health-care services known or perceived to be friendly to MSM if they fear or have experienced violence because they were believed to have male partners.¹⁸ Legal prohibitions against male–male sex are used by governmental and ethics institutions to justify prohibition of research into the most effective ways to deliver prevention services to MSM. Decriminalisation of male–male sex and development and implementation of antidiscrimination laws is crucial and has been called for by WHO.⁶

Despite criminalisation of same-sex behaviour in most African countries, several cross-sectional studies of HIV and STIs have been done in African MSM since 2005.^{3,57,89,90} Findings of poor knowledge of HIV and little access or exposure to prevention measures are of particular concern.⁹¹ Reaching out to MSM in research studies is achieved through involvement of trained MSM peer educators because MSM populations are often hidden and fear confrontations with health workers and confidentiality breaches.⁹² Engagement of grassroots MSM organisations and health stakeholders is necessary to build trust and ensure a safe environment. MSM have been reached and provided with on-going research services in coastal Kenya;⁹³ MSM peer engagement was used to promote uptake of HIV counselling and testing, and focused on an

improved understanding of the transmission risks associated with HIV and STIs, perceptions and experience of stigma, discrimination and violence, and knowledge; previous use; and beliefs about the efficacy of antiretroviral therapy.

In Asia, HIV prevention measures for MSM have been consolidated in a comprehensive package of services and include exposure to outreach programmes and targeted media and access to voluntary counselling and therapy, condoms and lubricants, services for STIs, enabling environments, training and infrastructure development, and strategic information.⁹⁴ However, coverage is much less than the 60–80% needed to have an effect on the HIV epidemic.^{81,95}

Expedition of the uptake of services (including prevention services) is a substantial challenge in settings where same-sex behaviour is strongly rejected by communities, traditional and cultural values expect men to marry and raise children, and frontline health workers have little or no skills in relation to open discussion of anal sex practices, diagnosis of rectal STIs, and support of specific prevention needs for MSM. Cultural competency training and training on the specific health needs of MSM are needed for health-care workers. Should health services for MSM be provided in separate facilities or integrated into general clinics? Integration offers the opportunity to lessen the stigma associated with seeking care but will necessitate broad consensus to develop appropriate clinical protocols and training for health-care providers. Anti-gay laws in some countries will probably be used to rationalise the absence of appropriate services and training of health-care providers on a large scale.

Conclusion

The next steps in HIV prevention in MSM will be technically difficult and costly. Proof-of-concept studies of combination prevention approaches should be followed by large, multicentre prevention trials of promising packages. To achieve this aim, innovative study designs and new networks of research capacity will be needed, especially in low-income and middle-income countries.⁷⁸ Furthermore, resources for scale-up and changes to laws and policies that frustrate the best practices of public health and HIV prevention will be needed.⁶ Generational investments are needed to improve the ways that medical providers are trained and to retrain those already qualified so that health care is medically and culturally competent for MSM.

Alteration of the trajectory of new HIV infections in MSM will necessitate a lot of work. New prevention approaches, increasing acknowledgment of HIV challenges in MSM worldwide, and emphasis on research and programmes for MSM in low-income and middle-income countries are promising signs. Better prevention strategies and a strong international commitment are needed to bolster this effort.

Contributors

PSS, AC-D, JS, AS, EJS, PG, IM, SMG, and TC developed the review framework and article structure. SMG did the modelling experiments. SMG, PSS, AS, and PG developed input parameters for modelling experiments. PS led the systematic review of published work. All authors contributed to the interpretation of the data and provided comments on the report at various stages in its development.

Conflicts of interest

We declare that we have no conflicts of interest.

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For more on training on the specific needs of MSM see <http://www.marps-africa.org>

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