Interventions to strengthen the HIV prevention cascade: a systematic review of reviews

Shari Krishnaratne, Bernadette Hensen, Jillian Cordes, Joanne Enstone, James R Hargreaves

Summary

Background Much progress has been made in interventions to prevent HIV infection. However, development of evidence-informed prevention programmes that translate the efficacy of these strategies into population effect remain a challenge. In this systematic review, we map current evidence for HIV prevention against a new classification system, the HIV prevention cascade.

Methods We searched for systematic reviews on the effectiveness of HIV prevention interventions published in English from Jan 1, 1995, to July, 2015. From eligible reviews, we identified primary studies that assessed at least one of: HIV incidence, HIV prevalence, condom use, and uptake of HIV testing. We categorised interventions as those seeking to increase demand for HIV prevention, improve supply of HIV prevention methods, support adherence to prevention behaviours, or directly prevent HIV. For each specific intervention, we assigned a rating based on the number of randomised trials and the strength of evidence.

Findings From 88 eligible reviews, we identified 1964 primary studies, of which 292 were eligible for inclusion. Primary studies of direct prevention mechanisms showed strong evidence for the efficacy of pre-exposure prophylaxis (PrEP) and voluntary medical male circumcision. Evidence suggests that interventions to increase supply of prevention methods such as condoms or clean needles can be effective. Evidence arising from demand-side interventions and interventions to promote use of or adherence to prevention tools was less clear, with some strategies likely to be effective and others showing no effect. The quality of the evidence varied across categories.

Interpretation There is growing evidence to support a number of efficacious HIV prevention behaviours, products, and procedures. Translating this evidence into population impact will require interventions that strengthen demand for HIV prevention, supply of HIV prevention technologies, and use of and adherence to HIV prevention methods.

Funding Bill & Melinda Gates Foundation.

Lancet HIV 2016; 3: e307–17

See **Comment** pages e284 and e286

Department of Social and Environmental Health Research (S Krishnaratne MSc, B Hensen PhD, J R Hargreaves PhD) **and Centre for Evaluation** (S Krishnaratne, J R Hargreaves), **London School of Hygiene & Tropical Medicine, London, UK; Department of Global Health, Emory University, Atlanta, GA, USA** (J Cordes); **and Public Health and Epidemiology, School of Medicine, Nottingham University, Nottingham, UK** (J Enstone)

Correspondence to: Shari Krishnaratne, London School of Hygiene & Tropical Medicine, London WC1H 9SH, UK **shari.krishnaratne@lshtm.ac.uk**

Introduction

Despite progress in development and delivery of efficacious HIV prevention interventions, more than 1 million people are newly infected with HIV every year.[1] UNAIDS have called for a reinvigoration of HIV prevention methods and suggest that 25% of global HIV spending should be allocated to prevention activities.[2] There is growing interest in the use of HIV prevention cascades to support the development and implementation of interventions and to facilitate resource allocation. In this issue, Hargreaves and colleagues[3] suggest a reframing of HIV prevention interventions organised around an HIV prevention cascade that can both integrate evidence from different disciplines and be more helpful for programmers. Garnett and colleagues[4] use observational data from Zimbabwe to operationalise the idea of an HIV prevention cascade as a monitoring tool. In this paper, we review the available evidence for HIV prevention as reflected in systematic reviews of HIV prevention interventions published during the past 20 years. We map the evidence base in line with the HIV prevention cascade, describe characteristics of interventions relevant to each area of the cascade, assess the type of evidence available on these interventions, and identify gaps and areas for future research.

Methods

Search strategy and selection of reviews

We did three independent systematic searches to identify systematic reviews of HIV prevention interventions published in English from Jan 1, 1995. Search terms included HIV/AIDS MeSH terms, "behav*" (behavioural review), "struct*" (structural review), "prevent*" and "intervention", and terms specific to each included biomedical intervention.

To identify systematic reviews of biomedical HIV prevention interventions, on Aug 15, 2014, we searched the Cochrane Library, MEDLINE, ISI Web of Knowledge, and ClinicalTrials.gov. The search findings were updated on July 20, 2015, when we extended the search to include Embase and no longer limited it to systematic reviews so that we could identify primary studies from 2012 that might not have been incorporated into reviews. To identify systematic reviews of behavioural interventions, on May 12–15, 2015, we searched the Cochrane Library, Embase, Health-Evidence.org, MEDLINE, and PsycNET

Research in context

Evidence before this study

We did a systematic review of reviews for domains across the HIV prevention cascade. Because we restricted our search to review articles, we are confident that we would have identified any additional reviews of reviews on a similar scale to this work. Our search identified several overviews of the literature on HIV prevention, but few systematic reviews of reviews. One review published in 2013 searched for and described evidence for HIV prevention interventions as they pertain specifically to young people and adolescents. We refer to the methods used in this review in our work, and we have based the appraisal and rating of the evidence in our review on that previous review.

Added value of this study

To our knowledge, this is the first review of reviews on HIV prevention of this size and scope. We map the evidence across the HIV prevention cascade and show strong evidence for the efficacy of biomedical tools such as of pre-exposure prophylaxis (PrEP) and voluntary medical male circumcision and for increasing supply of biomedical tools such as condoms or clean needles. By mapping the published work in this way, we present evidence in a format that we hope will be useful to programme developers and implementers and that will provide an evidence base to inform policy on HIV prevention.

Implications of all the available evidence

We highlight the importance of combination HIV prevention interventions that address structural and behavioural barriers to the uptake, use of, and adherence to strategies known to prevent HIV. Future research for biomedical tools with demonstrated efficacy should focus on population-level effectiveness. Research on increasing supply of these tools should use more rigorous study designs to measure impact in specific populations, including cluster randomised trials where feasible; if not feasible, a range of alternative impact designs are available. Although a range of interventions seek to address demand for HIV prevention, these have rarely been studied using experimental trials, and, where studied, have shown heterogeneous effectiveness. Similarly, studies of interventions to support use or adherence to HIV prevention need further adaptation and study aligned with the new HIV prevention cascade.

and for papers that described interventions implemented. To identify systematic reviews of structural interventions, we searched the Cochrane Library, MEDLINE, ISI Web of Knowledge, and Health-Evidence.org. We did the initial search for reviews about structural interventions on Aug 1–10, 2014, and updated the results on May 15, 2015.

Data were extracted from reviews with a data extraction tool (appendix 1) Reviews were eligible for inclusion if they systematically reviewed the evidence on the effectiveness of HIV prevention interventions. Reviews of experimental and observational studies were included. There were no restrictions on populations. We excluded broad overviews, scoping reviews, and unsystematic literature reviews.

See Online for appendix 1

See Online for appendix 2

We excluded reviews containing studies of behavioural interventions and structural interventions done only in high-income countries because we wanted to focus on areas in which HIV burden is highest and because the effectiveness of such interventions could be context specific and the heterogeneity of studies would present even greater challenges to data synthesis. We did not exclude any countries of implementation for reviews about the efficacy of biomedical products, because efficacy trials are not as heavily affected by contextual factors and so we considered the country-focus restriction less pertinent.

Primary study identification and data extraction

We extracted primary studies from reviews if they assessed at least one of the following outcomes: HIV incidence, HIV prevalence, reported condom use, and uptake of HIV testing. For studies of direct mechanisms only, HIV incidence had to be a primary outcome to qualify for inclusion. We included condom use and uptake of HIV testing as proximate outcomes of intervention effectiveness because these are two of the most commonly reported outcomes in studies that do not report biological HIV outcomes. Although prevention of mother-to-child-transmission interventions and outcomes were identified by some reviews, here we aimed to look specifically at sexual transmission or transmission through needle sharing.

We developed an approach for minimal data extraction at the primary study level (appendix 2); data included the country of focus, target population, study design, reported outcomes, and overall findings of each study. We classified reviews and primary studies with the HIV prevention cascade typology described by Hargreaves and colleagues.[3] Many primary studies fit into more than one category, but we allocated each study into one category only based on what we judged the most prominent component seemed to be, despite recognising that some interventions include components targeting more than one of three domains: demand-side, supply-side, and adherence (table 1).

The demand-side domain contained studies in which we judged the main aim of intervention to be to influence behaviour by targeting risk perception or strengthening awareness of, and positive attitudes towards, HIV prevention behaviours and technologies. These interventions include those providing information, education, and communication and those intended to influence perceived norms through peer-based approaches. Interventions were delivered in a range of settings and to different target populations.

The supply-side domain contained studies in which we judged the main aim of intervention to be to influence

the supply of HIV prevention products and messages. Examples included mass condom distribution, needle exchange initiatives mainstreaming HIV prevention within other services, and treatment strategies for sexually transmitted infections (STIs). Some, but not all, of these interventions have been characterised as structural interventions in published work.

The adherence domain contained studies in which we judged the main aim of intervention to be to support adoption or maintenance of prevention behaviours, including, but not restricted to, the use of prevention technologies. These interventions often sought to influence behavioural self-efficacy or skills and included interventions such as longitudinal risk counselling. We also included within this group interventions that targeted social determinants of behaviour hypothesised to act as barriers to the ability of individuals to access or adhere to prevention, such as cash transfers or livelihood interventions. Again, some of these interventions have been identified as structural in the published work.

Studies in the direct mechanism domain were most often individually randomised trials of the efficacy of biomedical products or procedures (eg, pre-exposure prophylaxis [PrEP] or medical male circumcision).

Within each of these domains, we identified specific types of interventions. In describing each intervention type, we categorised the evidence according to the target population (table 1). We assessed the type and direction of the evidence for each of the four outcomes based on study design and reported findings (appendix 2). We used a framework created by Mavedzenge and colleagues[5] in their review of the evidence for interventions for young people and adolescents. We first described the study designs in each category with use of the ratings A, B, or C on the basis of how many randomised controlled trials were published for a specific outcome (table 2). We then assessed how many studies had findings that suggested intervention effectiveness or not, assigning a score of 1–4 (table 2). Two reviewers (SK and BH) assessed the evidence for structural and behavioural interventions. Disagreements, although rare, were resolved after consultation and detailed review of the studies in question. One reviewer (JE) assessed the evidence for biomedical interventions.

Role of the funding source

The funder of the study had no role in data collection, data analysis, data interpretation, or writing of the report; however, the decision to focus only on evidence from low-income and middle-income countries for the behavioural and structural reviews was made, in part, by the funder. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Findings

We identified 88 eligible reviews (figure 1A),[6–93] from which we extracted 292 primary studies (figure 1B). Of 194 primary studies of demand-side, supply-side, or adherence interventions, 137 (71%) used observational study designs (figure 2). 34 (38%) of 90 randomised controlled trials (RCTs) were trials of direct mechanisms to prevent HIV. 24 (12%) of the studies classified as demand-side, supply-side, or adherence included HIV incidence or prevalence or both as primary outcomes, whereas almost all (88%) reported condom use.

54 primary studies from 40 reviews contributed evidence for information, education, and communication interventions (table 3). The interventions included many different approaches to influence risk perception, awareness, and attitudes about preventive behaviours, including through multimedia, text messages, posters, and other forms of communication. For example, the Helping Each Other Act Responsibly Together (HEART) campaign in Zambia included a multimedia programme of television spots, public service announcements, radio advertisements, music videos, posters, and billboards to share messages about HIV and STI risk reduction.[94] A secondary-school-based programme in KwaZulu-Natal provided sexual health and HIV prevention messages through either drama performances or an information

	Intervention type	Subcategory (if applicable)
Demand-side interventions	IEC	Young people, men, women, people who use drugs, mass media
	Peer	Young people, men who have sex with men, female sex workers, people who use drugs or alcohol, general
Supply-side interventions	Integration of HIV services	..
	Needle or syringe programmes	..
	Condom distribution	..
	Community-level STI interventions	..
Adherence interventions	Counselling	Couples-based counselling, HIV testing and counselling, individual-level counselling, HIV-positive prevention
	Socioeconomic	Microfinance interventions, cash transfer interventions
Direct mechanisms of HIV prevention	Voluntary medical male circumcision	Male to female transmission, female to male transmission, men who have sex with men
	Condoms	..
	PrEP	..
	Microbicides	..
	STI treatment	..
	Vaccines	..

IEC=information, education, and communication. PrEP=pre-exposure prophylaxis. STI=sexually transmitted infections.

Table 1: **Categorisation of evidence of HIV prevention interventions in line with the HIV prevention cascade**

	3 or more RCTs (might also include observational studies)	1–2 RCTs (might also include observational studies)	No RCTS; only observational studies
Consistently showed effectiveness	A1	B1	C1
Largely, but not consistently, showed effectiveness	A2	B2	C2
Mixture of beneficial and ineffective or harmful results	A3	B3	C3
Consistent ineffective or harmful results	A4	B4	C4

RCT=randomised controlled trial.

Table 2: **Assessment of strength of evidence of HIV prevention interventions across types of interventions**

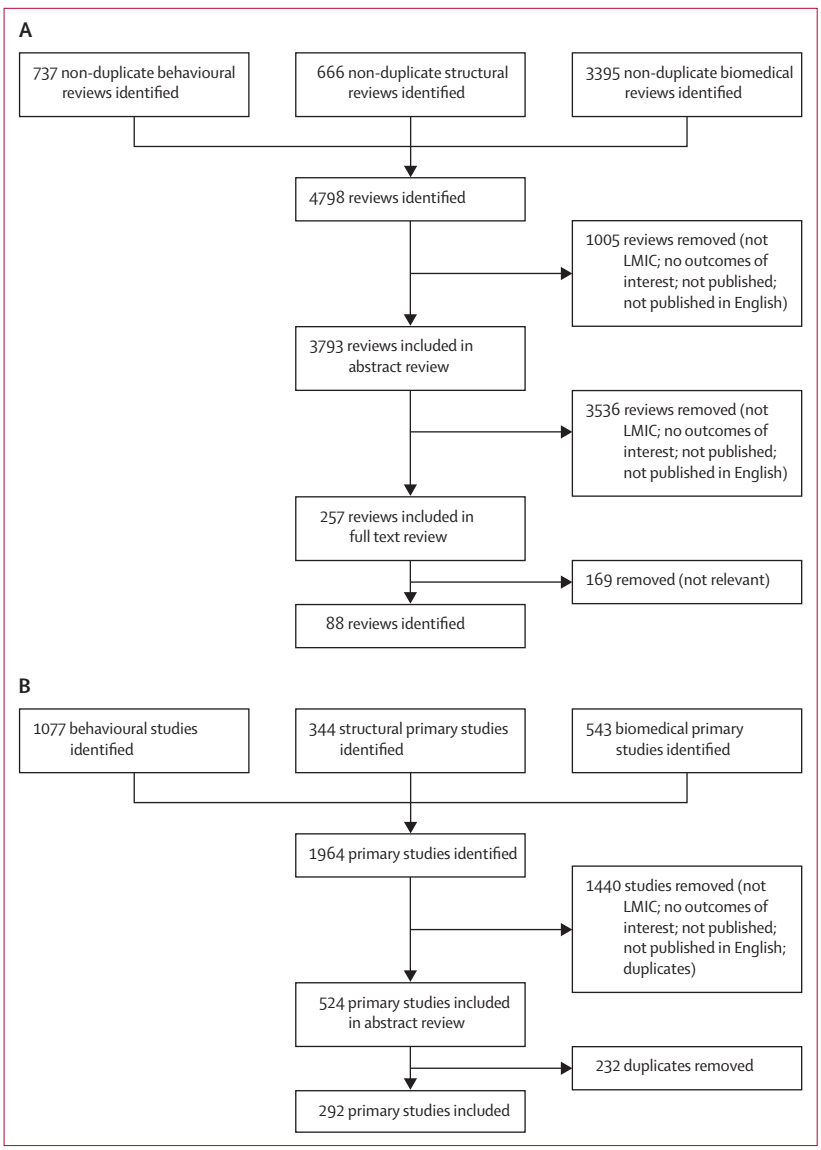

Figure 1: **Identification of systematic reviews (A) and primary studies (B) of HIV prevention interventions**
LMIC=low-income or middle-income country.

booklet, both delivered in classroom settings.[95] Slightly more than half (56%; n=30) of the information, education, and communication studies were of interventions focused on young people. An example is the MEMA Kwa Vijana cluster RCT of an intervention that provided primary school students with sexual health education through a participatory, teacher-led programme combined with training for health workers to provide sexual health services that are friendly to young people, as well as condom promotion and provision and community mobilisation.[96] Almost all studies of information, education, and communication interventions assessed condom use as a primary outcome (table 3).

31 reviews contributed 54 studies of peer-based interventions (table 3). Interventions in this category often combined peer-delivered sexual health education with either increased availability of direct mechanisms to prevent HIV, such as condoms, or community empowerment approaches. Studies of interventions targeted at female sex workers used peer-led community empowerment approaches to support mobilising female sex workers and developing a sense of community. An example is a peer-delivered education programme among establishment-based female sex workers in the Philippines, which combined venue-manager training with information on HIV and condom use.[97,98] Studies assessing the impact of these interventions on HIV incidence and prevalence among female sex workers used experimental and observational designs, but they showed little evidence to support their effectiveness on reducing HIV incidence or prevalence (table 3). 12 studies described peer-based interventions among young people. Examples include a project in Kenya that involved peer educators teaching students about HIV and life skills with songs, quizzes, competitions, and other methods; and Stepping Stones, an intensive community training programme designed for HIV-vulnerable communities in low-income countries. The participatory learning approach sought to empower men and women to take greater control over their sexual and emotional relationships.[99,100]

12 reviews contributed 35 studies on supply-side interventions (table 3). Approaches were often facilitated by policy changes, such as to increase access to free clean needles or subsidised condoms for populations most at risk (table 3). In Thailand, the 100% condom-use policy launched in 1989 promoted the practice of "no condom–no sex" in all types of sex work through collaborations between local authorities, sex business owners, and sex workers.[101] Similar approaches have been implemented in the Dominican Republic and Cameroon,[102,103] and adaptations for other population groups such as young people have also been attempted. Among the 20 primary studies describing the effectiveness of condom distribution interventions, three measured HIV prevalence, and all used observational study designs. Among six observational primary studies of exchange programmes for clean needles and syringes, three assessed HIV incidence as an outcome. Findings from one study supported effectiveness, whereas two did not (C3; table 3). Two observational studies measured HIV incidence and demonstrated findings in support of the intervention (C1). Three studies (all RCTs) described interventions aimed at STI control. These interventions aimed to increase access to STI testing and treatment. For example, in Rakai, Uganda, an intensive STI control programme via home-based mass antibiotic treatment was rolled out and studied in a cluster RCT design.[104]

16 reviews provided 51 studies of interventions to support the adoption and maintenance of prevention behaviours by influencing efficacy and skills through counselling-based interventions or interventions targeting

socioeconomic determinants. 26 primary studies described use of counselling alone or with HIV testing to promote HIV prevention. Seven reviews contributed evidence from studies describing couples-based counselling interventions (n=10). One observational study assessed the effect of couples-based counselling on HIV incidence with findings in support of the intervention (C1; table 3). Nine studies, including three RCTs, assessed self-reported condom use after couples counselling and findings from these studies were in support of the interventions (A1; table 3). Counselling interventions were most often delivered via health facilities through interactions between providers and patients or in community settings by providing either individual, couple-based, or group-based behavioural strategies to reduce HIV risk behaviours. 12 studies (seven RCTs) assessed individual-level counselling interventions. One example is a programme in South Africa that focused on people without HIV and delivered a 60-min risk-reduction counselling session led by health educators and delivered within a health-care setting.[105] Seven studies (four RCTs) assessed HIV-positive prevention counselling. For example, an RCT in South Africa studied an intervention that consisted of patient-centred discussions between counsellors and patients living with HIV during regular clinical visits focused on HIV risk reduction and tailored to specific patient needs.[106]

Interventions to address socioeconomic barriers to adherence to HIV prevention behaviours or other direct prevention mechanisms were based either on incentives or cash payments or on strengthening livelihoods through microfinance or related initiatives. Cash transfer interventions aimed to improve school attendance and educational outcomes and through this mechanism reduce HIV infection rates among young people.[107] Other interventions used a contingency management model, such as that in smoking cessation programmes, in which regular behaviour monitoring was combined with financial incentives when the desired behaviour was demonstrated.[108] Livelihood interventions involved training of participants in the development of products or services, access to markets, financial skills, and financial support or credit. The interventions sought to strengthen livelihoods among participants to alleviate poverty and increase self-efficacy. Microfinance interventions included the provision of small loans, assistance with the facilitation of income-generating activities, or provision of financial services.[61] In some cases, interventions were combined with life-skills interventions and condom distribution including in studies from Kenya and Zimbabwe.[109,110]

29 systematic reviews (in 28 publications) incorporated 98 primary studies of six direct mechanisms to prevent HIV (table 3). 38 studies, including three large RCTs, assessed the impact of medical male circumcision on HIV acquisition in heterosexual men (A1; table 3).[66] Cohort studies pre-dating the trials also indicated a protective effect for heterosexual men, including those at high risk.[67] A systematic review and meta-analysis covering seven primary studies, including one RCT, did not provide evidence of a protective effect of male circumcision for women (B3).[75] Four reviews provided 19 primary studies exploring whether circumcision protects men who have sex with men (MSM). No RCTs were found, but two subanalyses of observational data by partner role suggest, to varying extents, that circumcision might give a protective effect for MSM with a predominantly or exclusive insertive role.[76,77]

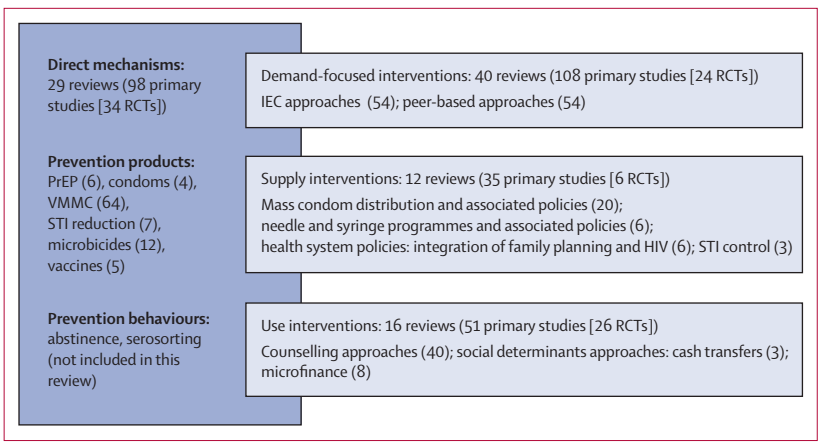

***Figure 2*: Mapping evidence for the HIV prevention cascade**
RCT=randomised controlled trial. PrEP=pre-exposure prophylaxis. VMMC=voluntary medical male circumcision. STI=sexually transmitted infections. IEC=information, education, and communication.

Two reviews describe evidence from six RCTs done between 2007 and 2009 to assess the effect on HIV incidence of oral PrEP (of daily tenofovir disoproxil fumarate, with or without emtricitabine, *vs* placebo).[82–84] Four trials showed findings in support of the intervention, with an efficacy of up to 75%, whereas two, which included women only, did not show any effect (as was also the case in the more recent VOICE trial. One RCT assessed the efficacy of PrEP on HIV incidence among people who inject drugs (B1) and one assessed the efficacy of PrEP on HIV incidence among MSM (B1). This latter RCT, the iPrEx trial, was done in six countries and involved approximately 2500 men comparing daily tenofovir disoproxil fumarate plus emtricitabine versus placebo and demonstrated a positive effect on incidence.[111]

We identified five RCTs of HIV vaccines in two reviews. One trial (RV144), a large trial conducted in 2009 in Thailand with the ALVAC-HIV vaccine and AIDSVAX B/E boosters, demonstrated moderate efficacy.[112] In a modified intention-to-treat analysis, vaccine efficacy was 31·2% (95% CI 1·1–52·1). Other vaccines trialled have not protected against HIV infection or reduced viral load, including the MRKAd5 HIV-1 gag/pol/nef subtype B vaccine used in the Step and Phambili studies, which was discontinued at interim analysis because it showed no protective effect.[113,114]

	Incidence		Prevalence		Condom use		HIV testing	
	Number of studies	Quality assessment rating	Number of studies	Quality assessment rating	Number of studies	Quality assessment rating	Number of studies	Quality assessment rating
Demand-side interventions								
Effect of IEC interventions focused on young people[6–19]	3 (1)	B4	1 (1)	B4	28 (7)	A3	..	..
Effect of IEC interventions focused on men[12,13,20–23]	..	..	..	..	9 (3)	A2	1 (0)	C1
Effect of IEC interventions focused on women[21,23]	..	..	..	..	2 (2)	B3	..	..
Effect of IEC interventions using mass media[7,12,14]	1 (1)	B3	..	..	9 (1)	B4	..	..
Effect of IEC interventions focused on people who use drugs[16,22,24]	..	..	..	..	4 (3)	A1	..	..
Effect of peer-based interventions focused on young people[6,8,10,13,15,16,25–30]	1 (1)	B4	..	..	11 (0)	C2	2 (0)	C1
Effect of peer-based interventions focused on MSM[30–36]	..	..	..	..	3 (1)	B1	1 (0)	C1
Effect of peer-based interventions focused on female sex workers[9,14,18,28,30,37–44]	3 (1)	C4	4 (0)	C4	22 (3)	B2	3 (0)	C1
Effect of peer-based interventions focused on people who use drugs or alcohol[22,28,30,32,45–47]	2 (2)	B4	1 (1)	B4	5 (2)	B3		
Effect of peer-based interventions with no population focus[9,18,22,28,30,32,33,43]	..	..	..	..	10 (2)	B1	1 (0)	C1
Supply-side interventions								
Effect of interventions that integrate HIV services into routine care[41,48]	..	..	..	..	1 (0)	C1	5 (0)	C1
Effect of clean needle or syringe programmes[49,50]	2 (0)	C3	6 (0)	C1	..	..	..	..
Effect of condom distribution interventions[7,9,15,18,20,44,51]	..	..	3 (0)	C1	20 (5)	A1	..	..
Effect of community-level STI interventions[52]	3 (3)	A4	..	..	1 (1)	B4	..	..
Adherence interventions								
Effect of couples-based counselling[45,53–57]	1 (0)	C1	..	..	9 (3)	A1	4 (3)	A3
Effect of HIV testing and counselling[14,21,53,54,58]	1 (1)	B4	..	..	8 (1)	B2	3 (2)	B1
Effect of individual-level counselling[14,16,22,24,37–39]	1 (1)	B3	..	..	12 (7)	A1	2 (1)	B3
Effect of HIV-positive prevention counselling[22,24,53,56,59,60]	..	..	..	..	7 (4)	A3	..	..
Effect of microfinance interventions[61–64]	1 (1)	B4	..	..	8 (4)	A3	1 (1)	B1
Effect of cash transfer interventions[65]	2 (2)	B4	2 (2)	B1	1 (1)	B4		
Direct mechanisms								
Medical male circumcision for heterosexual route risk (female to male)[66–74]	38 (3)	A1	..	..	..	..	..	..
Medical male circumcision for heterosexual route risk (male to female)[72,75]	7 (1)	B3	..	..	..	..	..	..
Male circumcision men who have sex with men route individual-level studies[71,76–78]	19 (0)	C3	..	..	..	..	..	..
Condoms (heterosexual) individual-level studies[79–81]	4 (0)	C1	..	..	..	..	..	..
Oral PrEP (overall) individual-level studies[82–84]	6 (6)	A2	..	..	..	..	..	..
Microbicide prophylaxis individual-level studies[48,71,85–90]	12 (12)	A3	..	..	..	..	..	..
STI treatment individual-level studies[44,84,89,91–93]	7 (7)	A4	..	..	..	..	..	..
HIV vaccine individual-level studies[71,88]	5 (5)	A3	..	..	..	..	..	..

In cells showing the number of studies, numbers in parentheses are randomised controlled trials. IEC=information, education, and communication. STI=sexually transmitted infections. PrEP=pre-exposure prophylaxis.

Table 3: **Number and type of studies describing HIV prevention interventions and the impact of these interventions on key outcomes**

Discussion

We found evidence from several randomised trials in support of the efficacy of direct mechanisms to prevent HIV. Evidence also suggests that supply-side interventions that increase access to these efficacious technologies can be effective, and that there is a need for continued research on interventions to increase demand for and adherence to direct mechanisms to prevent HIV. As the cascade highlights, demand, supply, and use of interventions are all crucial domains to increases in uptake of and adherence to direct HIV prevention mechanisms. The interventions and combination of interventions required to translate the efficacy of direct mechanisms into population-level impact will require monitoring for these domains to understand gaps and support intervention development.

HIV prevention technologies such as male and female condoms or clean injecting equipment have existed for several years. In recent years, evidence for the efficacy of other direct mechanisms, including medical male circumcision and oral PrEP, has emerged. Much is left to learn about how these mechanisms increase coverage and support adherence to achieve population-level impacts. Our review identified a range of potential interventions addressing these elements of the cascade. Supply-side interventions, such as mass condom distribution and needle and syringe exchange initiatives, have shown impact on use of these methods. However, relatively few studies have explored the effect of these interventions on HIV outcomes, and where these were studied, randomised trials have rarely been used.

Findings from demand-side interventions such as information, education, and communication and peer-based interventions on HIV outcomes have been disappointing, with these interventions rarely reducing HIV incidence or prevalence. Few trials and studies identified in the reviews evaluated interventions to increase demand for medical male circumcision or adherence to PrEP, although evidence for this domain is emerging.[115,116] There remains a need for additional research to understand why, despite supply, there is low uptake of these strategies and for evaluations of novel interventions to increase this uptake and adherence. With evidence arising on how to increase demand for medical male circumcision, systematic reviews of such strategies are warranted. As new direct mechanisms, including microbicides and vaccines, emerge, lessons learned from existing interventions could improve access.[116]

The evidence for the effectiveness of supply-side interventions is a timely reminder of the gains that can be made in HIV prevention by making prevention products accessible and available to populations in need. In circumstances where social barriers threaten efforts to reduce HIV incidence, these interventions can be effective at increasing access to HIV prevention methods and possibly reducing incidence. Policy changes are sometimes necessary to create the platforms to ensure biomedical and behavioural interventions reach and can be used by those who need them at scale. Overall, our review draws similar conclusions to Mavadzenge and colleagues:[5] there is some evidence that in-school interventions can have an impact on some HIV outcomes, and there is proven efficacy of several biomedical HIV prevention tools.

Our mapping of the literature highlights that distinction between the structural and the behavioural has not clearly distinguished interventions, and that classifying interventions this way might have created some confusion. For example, Stepping Stones was identified in reviews of interventions targeted at young people and women and in a review to explore the effect of this intervention on individual biological outcomes through to structural level changes in gender norms.[100] Similarly, an intervention of social marketing to youth for condom use was included in reviews identified through the behavioural search and the structural search.[103] These examples highlight that defining the level at which an intervention operates might be less useful than would categorising it by the objective of the intervention (eg, to increase demand for HIV prevention or support adherence).

Our review also shows the many gaps that still exist in the literature on the effectiveness of interventions for HIV prevention, particularly when it comes to demand-side, supply-side, and adherence interventions. Although we identified a large number of studies across these typologies, most were observational in design and often relied on self-reported behavioural outcomes. This might be interpreted as meaning that these studies contribute less to the evidence base for effectiveness than do those using randomised trial designs. However, observational studies are necessary and important when randomisation is either not feasible or even unethical, providing strong evidence that an intervention likely had an effect if the design is robust. As stated, our goal here is to describe the current state of HIV prevention research and to highlight key research gaps. As such, it is necessary to describe the evidence from these studies, alongside that from studies with more robust study designs to accurately map the state of the evidence.

Our mapping method has several limitations. First, our search strategy might have missed reviews of prevention technologies. However, in light of the large overlap found between the primary studies included in the reviews, we consider it unlikely that this would have led to us excluding a large number of relevant primary studies or have affected our overall conclusions. Second, because we carried out a review of reviews, we only assessed studies that were themselves included in a systematic review (no extra studies of biomedical HIV prevention interventions were included when we opened the search to primary papers). Such an approach will inevitably miss recently published studies. For example, the FACTS 001 trial, a phase 3, multicentre RCT in South Africa that evaluated the safety and effectiveness of pericoital tenofovir 1% gel, announced trial results in early 2015 and was therefore not included in any systematic reviews we identified. The study found no evidence of an effect on HIV incidence.[117] Results of two trials showing efficacy of oral PrEP in MSM were also published after our search.[118,119] The one review we identified that described cash transfer interventions included 16 studies, but at the time of publication, only three studies had reported relevant data on HIV-related outcomes. Subsequently, findings from at least one study, the HPTN 068 trial, have been released.[120]

Third, we identified a large number of primary studies of complex interventions that had components aimed at increasing demand through information, education, and communication and peer interventions. We aimed to map interventions to the HIV prevention framework by

the main intervention component. However, classification was subjective and reviewers might classify interventions differently or might have opted to categorise interventions into multiple categories. The implications of this are that we might under-report available evidence in a certain category. We opted to classify studies into only one category to avoid overstating the evidence available on HIV prevention interventions. Additionally, two reviewers discussed classification in detail and consulted a third if there was strong disagreement and so it is unlikely that any misclassification would change our findings substantially.

Fourth, where possible, we discussed the available evidence for biological HIV outcomes. However, self-reported behavioural outcomes were often the only measure of intervention effect presented in studies, particularly those describing demand-side, adherence, and supply-side interventions. Such outcomes have insufficient ability to show actual changes in behaviour; however, only including studies that reported biological HIV outcomes would have vastly reduced the number of primary studies assessed. The inclusion of studies assessing condom use as an outcome allows us to describe evidence from key interventions that align with the prevention cascade. By including these studies, we highlight evidence showing that interventions do influence proximate measures of demand, supply, and adherence.

Finally, our objective was to do a systematic review of systematic reviews. Our objective was not to assess the methodological rigour of the primary studies identified by these reviews. Our decision to categorise primary studies, rather than the reviews themselves, into the specific cascade domains was led by the large overlap across primary studies included in the reviews. As such, our review provides an overview of the rigour and strength of the evidence; however, it does not provide nuanced detail of the quality of the primary studies.[5] Given the minimal data extraction that we did at the level of the primary study, we cannot comment on heterogeneity across populations included in the studies. We appreciate that it is important to understand whether populations in studies with robust study designs and showing consistent effectiveness are similar or different to those in studies using mostly observational study designs, and demonstrating inconsistent or no effectiveness. Understanding the potential relationship between evidence quality and the populations studied is an important next step. Again, our objective was not to critically appraise primary studies or specific interventions but to map where along the prevention cascade evidence of interventions is available, the number and type of studies, and whether these studies generally supported the intervention or not. A primary goal was to highlight areas in which more research is needed.

The current evidence base on HIV prevention shows that we have methods that work at the individual level, and that the goal of ensuring population-level effect is achievable through the use of interventions that support demand for HIV prevention, supply of HIV prevention technologies, and adherence to the direct mechanisms that prevent HIV. The use of an HIV prevention cascade that includes these domains provides a framework to understand why a proven direct mechanism is failing to have a population-level impact and support the development and implementation of interventions to target these domains. Systematic reviews that explore the current evidence in the four categories identified in this paper should be done to understand fully what works, for whom, and under which circumstances. This is an essential next step for the evidence mapping we have initiated here. Future research that builds on the current evidence base and shows approaches to gaining impact for HIV prevention methods is necessary to ensure intervention effectiveness.

Contributors

SK did the search for structural reviews, developed the data extraction forms at the review and primary study level, extracted data at the review and primary study level for structural and behavioural reviews, did the evidence assessment, and contributed to the writing of the manuscript. BH conducted the search for behavioural and structural reviews, extracted data at the review and primary study level for behavioural reviews, did the evidence assessment for structural and behavioural reviews, and contributed to the writing of the manuscript. JC assisted with data extraction at the review and primary study level for behavioural reviews. JE did the search for biomedical reviews, extracted data at the review and primary study level for biomedical reviews, did the evidence assessment for biomedical reviews, and contributed to writing of the manuscript. JRH and SK conceived the idea for this paper, as commissioned by the funding source. JRH contributed to the writing of the manuscript, provided the framework upon which the evidence in this review is mapped, and provided oversight throughout all aspects of the review and writing process.

Declaration of interests

We declare no competing interests.

Acknowledgments

This paper was funded by the Bill & Melinda Gates Foundation through Chariot Innovations (London, UK). The Foundation commissioned a landscaping review of the evidence on HIV prevention. The Foundation has requested that this review be submitted as part of a series on HIV prevention to be published in this journal. SK and JE received grants from Bill & Melinda Gates Foundation during the conduct of the study. Contributions from London School of Hygiene & Tropical Medicine authors are part of their work for the Centre for Evaluation, which aims to improve the design and conduct of public health evaluations through the development, application and dissemination of rigorous methods, and to facilitate the use of robust evidence to inform policy and practice decisions.

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