HIV prevention transformed: the new prevention research agenda

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We have entered a new era in HIV prevention whereby priorities have expanded from biomedical discovery to include implementation, effectiveness, and the effect of combination prevention at the population level. However, gaps in knowledge and implementation challenges remain. In this Review we analyse trends in the rapidly changing landscape of HIV prevention, and chart a new path for HIV prevention research that focuses on the implementation of effective and efficient combination prevention strategies to turn the tide on the HIV pandemic.

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Introduction

Until recently, HIV prevention lacked credibility with data from prevention trials showing little or no decrease in incident HIV.[5] Furthermore, when successes were made public,[6–8] explanations were often conflicting and lessons for application to other settings unclear. However, the past year marked the end of this steady stream of disappointing results, and a concomitant change is evident in public perception and the opinions of policy makers. The discourse on HIV prevention now includes the possibility that the epidemic can be stopped.[9]

Increasingly scarce financial resources also drive this renewed focus on prevention. The global economic crisis has substantially affected funding for HIV, with resources for prevention levelling off in the past decade and future funding commitments unclear.[10] These reductions put many programmes at risk and warrant a sharpened focus on prevention. Fiscal constraints have created pressure on prevention programmes to be more accountable by providing clearer evidence of impact and delivering better value for money.

We review developments in HIV prevention from the past 3 years (since *The Lancet* Series on HIV prevention in 2008[2–4]), with particular emphasis on gaps in knowledge and a focus on what are now the most salient prevention issues: discovery in the continued search for vaccines and a cure; new challenges related to antiretroviral-based prevention; implementation challenges that preclude scale-up of prevention strategies known to be effective—specifically, HIV testing, voluntary medical male circumcision (VMMC), and prevention of mother-to-child transmission (PMTCT); and progress on and challenges for structural and behavioural interventions.

Vaccines and the search for a cure

Strategies for vaccine development include innate, cell-mediated, or antibody-mediated resistance to infection, or all three.[11] Successful modification of HIV in Rhesus macaque monkeys led to increased focus on cell-mediated immunity;[12] however, the STEP trial[13] (using immunogens that worked in macaques) showed neither protection from HIV nor alteration in viral replication in vaccine recipients, but did stimulate an immune response that exerted pressure on the virus acquired.[14] In a trial in Thailand[15] a canarypox vector vaccine (ALVAC-HIV) boosted with a recombinant glycoprotein vaccine (AIDSVAX B/E) led to a 31% reduction of HIV incidence in vaccine recipients. The immune responses that enabled protection are a focus of intensive post-trial studies, including consideration of non-neutralising antibodies that function via antibody-dependent cellular cytotoxic effects (ADCC).[16,17]

Renewed interest[18] in curing HIV was partly stimulated by a report of a bone-marrow transplant of *CCR5*-deleted stem cells to an HIV-positive patient, who seemed to eliminate detectable HIV after engraftment of this tissue.[19] This result confirmed the importance of the *CCR5* receptor for HIV replication, and galvanised experiments focused on gene therapy to modify this receptor, to date conducted ex vivo and in a mouse model.[20] Investigators committed to curing AIDS have further divided this work into immunomodification[21] and the use of antiretroviral drugs to eliminate all HIV-infected cells.[22] For both approaches, the latent reservoir of HIV-infected T cells is the greatest challenge. At the start of HIV infection, the virus is integrated into host DNA, and cells become quiescent and allow HIV replication at a very low rate, even with antiretroviral therapy (ART).[23] However, when ART is discontinued, viral load returns to a level recorded before therapy. A novel class of cancer drugs designed to

Search strategy and selection criteria

We covered several topics in HIV prevention (biomedical, behavioural, structural) that together comprise combination prevention.[1] We focused on randomised trials, rigorous observational studies, and systematic and meta-reviews completed since *The Lancet* Series on HIV prevention in 2008.[2–4] The most recent reviews[5] were used as a starting point. We searched PubMed and Medline for papers published in peer-reviewed journals since 2008, and electronic conference proceedings of recent HIV/AIDS-related conferences up to the end of April, 2011. We also reviewed relevant publications and websites from international organisations, including UNAIDS and WHO, and non-governmental organisations and advocacy groups involved in HIV prevention research. Search terms included "HIV", "prevention", "antiretroviral therapy (ART)", "vaccines", "behavior", "HIV testing", "male circumcision", "microbicides", "mother-to-child transmission (MTCT)", "implementation science", and "operations research". Because the effectiveness of a single intervention was not the objective of the review, systematic review methods were not used. The goal was instead to broadly review existing prevention interventions and identify salient issues, research needs, and gaps in knowledge.

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force replication in each infected cell in the latent pool (so traditional ART can work) is now entering clinical trials.[22]

An alternative to eradication of HIV is a so-called functional cure of infection that is evoked by stimulation of T cells to restrict HIV replication in the absence of antiretroviral drugs. Intensive studies of the HIV response to T cells in acute infection,[24] and of the few patients whose immune systems control HIV,[25] suggest the feasibility of this approach with a combination of immunogenic proteins (a therapeutic vaccine), immunostimulatory cytokines, and other novel forms of immune modification of the virus by reactive T cells.[26] Patients treated very early might have a smaller pool of latent virus, and might therefore be good candidates for such curative therapy.[22]

Product development and proof-of-concept studies are important areas in the search for HIV vaccines and a cure. The next phase of vaccine research will focus on development of immunogens that allow the HIV-negative recipient to form durable neutralising antibodies.[27] Protection of Rhesus macaques from simian immunodeficiency virus (SIV) was possible with the passive infusion of monoclonal antibodies that neutralise SIV.[28] Additionally, Stamatatos and colleagues[29] and Tomaras and colleagues[30] described the detection of very broad and potent neutralising antibodies in a patient with HIV infection. However, such antibodies are generated too late to affect the disease.[27] These findings could facilitate the design of a vaccine that leads to secretion of high concentrations of protective antibodies in the genital tract, whether neutralising or ADCC.[11,16] Another innovative approach is passive immunisation, either by direct administration of broadly neutralising antibodies, or by use of gene transfer technology to achieve sustained production of antibodies. In the search for a cure, experiments using vaccination, maximal ART, and adjunctive cytokines are in progress, and are the subject of the Martin Delaney cure award.[31–33]

Prevention based on antiretroviral drugs

Pre-exposure prophylaxis

Concerted and ongoing efforts aim to understand the penetration of antiretroviral drugs into the male and female genital tract, and the protective effects of oral or topical (ie, microbicide) pre-exposure drugs on HIV acquisition.[34] The first results were reported in 2010, in the CAPRISA 004 study in South Africa.[35] 889 high-risk women used an applicator that delivered 1% tenofovir gel into the vaginal vault up to 12 h before, and within 12 h after, intercourse. Investigators reported a 39% reduction in overall acquisition of HIV, and maximum reduction was 54% in the most adherent women. HIV acquisition was inversely correlated with detection of tenofovir in the vaginal secretions—an indication of the strong association between product adherence and efficacy. An ongoing trial[36] further examines these results by examining daily use of gel and oral pre-exposure prophylaxis, and compares these regimens with placebo. Tenofovir gel also inhibits replication of herpes simplex virus-2 (HSV-2), and reduced acquisition of this virus was noted in CAPRISA.[35]

Eight trials with oral antiretroviral agents for pre-exposure prophylaxis are currently ongoing,[37] using antiviral agents that proved protective in a macaque model.[38] In the iPrEx study in 2010,[39] HIV-negative men who have sex with men were given daily emtricitabine and tenofivir disoproxil fumarate (TDF plus FTC) for up to 2·8 years. This antiretroviral combination was selected because it offered the greatest protection to Rhesus macaques in a model of rectal exposure.[38] The study recorded a 44% reduction in HIV acquisition and, as with CAPRISA,[35] efficacy was strongly associated with concentrations of antiretroviral drug, which is a direct marker of adherence. Some study participants had mild renal dysfunction or decrease in bone mineral density, and two who had unrecognised acute (seronegative) HIV infection on pre-exposure prophylaxis developed a antiretroviral-resistant variant. By contrast, the FEM-PrEP trial of TDF plus FTC offered to high-risk women was discontinued because an equal number of infections occurred in both the placebo and treatment groups.[40] The precise explanation for the difference between the IPrEx and FEM-PrEP results is unknown; however, a strong possibility is that the concentration of tenofovir in the female genital tract is insufficient to prevent HIV acquisition.[41,42] These results do not diminish the potential for oral pre-exposure prophylaxis, but recommendation of wide-scale promotion for women would be premature.

Treatment for prevention

Treatment for prevention describes the public health or community benefits from the use of ART to decrease onward transmission of HIV.[43] The biological mechanism is that treatment reduces viral load and thus reduces infectiousness.[44] Five observational reports noted substantial reduction of HIV transmission to a sexual partner when the HIV-infected index case was given ART.[45] The HPTN 052 study[46] is a randomised controlled trial that directly examines the ability of ART to interrupt HIV transmission from an index patient with HIV to his or her sexual partner. On April 28, 2011, the multinational Data Safety and Monitoring Board overseeing the study reported a substantial difference in prevention and treatment outcomes related to early start of ART, and recommended that the randomisation study be ended. Findings from the study showed a 96% reduction of HIV transmission attributed to the use of antiretroviral drugs.[47]

Some (but not all) results from mathematical modelling analyses lend support to the population-level use of treatment for prevention[48,49] and suggest a greater benefit than that possible with pre-exposure prophylaxis.[50] Guidelines for HIV treatment support early start of ART,[51] which would also favour the public health potential of this approach, and several population-level pilot studies of antiretroviral drugs for prevention are now planned. Importantly, the HPTN 052 trial has bridged a crucial

gap by unequivocally showing that treatment for prevention is efficacious.

Key research areas for prevention with antiretroviral drugs

The extent to which pre-exposure prophylaxis and ART reach individuals with the highest viral load is central to the success of prevention approaches based on antiretroviral drugs. The main challenge is whether the right people have the right drug concentrations of the right drugs at the right time.[17] Hence, an important issue for both pre-exposure prophylaxis and treatment for prevention is to establish eligibility, for which high and frequent uptake of HIV testing is a requisite. In treatment for prevention, the difficulty in detection of people with HIV infection who are asymptomatic has been well documented.[52,53]

Another approach is to emphasise ART access before the rise in viral load that typically occurs in late stages of infection, especially in patients with the highest viral loads[54]—eg, those with early infection who are the most infectious.[17] Patients with acute and primary HIV infection have also been difficult to identify, even though most are symptomatic.[17] Although new diagnostic approaches might overcome some of these challenges,[55] the difficulty of linking asymptomatic people to care has been well documented.[44,43,56]

Another important issue, given challenges related to universal access, is how to prioritise distribution of antiretroviral drugs. Most agree that pregnant women in Africa and discordant couples are high-priority groups, but the need extends far beyond these groups. Moreover, the potential role of pre-exposure prophylaxis in these groups should be tempered by the findings of the FEM-PrEP study.[40] The most crucial issue for distribution is how to ensure that equity considerations are appropriately addressed in resource-poor settings when treatment is not available to all who need it.

The burden of adding antiretroviral-based prevention to already strained health systems remains to be determined. The frail health infrastructure of sub-Saharan Africa, characterised by severe shortages in structural and human resources, is widely recognised as one of the main challenges in addressing the epidemic. To confront this issue, task shifting (ie, redistribution of tasks from highly trained health workers to those with less training, including non-professionals) is becoming more widespread.[57,58] Such reorganisation also decentralises health services (eg, to rural areas), reducing the travel burden to attend hospitals or clincs. Although task shifting is an efficient strategy with many documented successes, it presents many challenges, including the provision of training and supervision that is sufficient to maintain quality and safety, and the need to address resistance from governments and health professionals. However, task shifting is not a substitute for much needed resources and investments in health systems throughout the area.

As is apparent from the CAPRISA[35] and iPrEx[39] trials, adherence is a key issue, and research continues to examine innovative real-time strategies to monitor adherence to ART that could increase the reliability of adherence measures while increasing uptake.[59] Development of interventions that are less dependent on adherence (eg, rings, implants, longacting antiretroviral drugs, and slow-release topical approaches) is one of the crucial challenges.[60] Adherence is also a challenge for treatment for which approaches independent of adherence are needed. Research now aims to assess topical and systemic intervention products that differ from products used for treatment, well tolerated products, and the use of products for postexposure prophylaxis.[61]

Effective prevention strategies dominated by implementation challenges

HIV testing

HIV testing is recognised as a crucial part of almost all programmes for HIV prevention, especially in view of new developments in prevention with antiretroviral drugs. Testing can identify people living with HIV/AIDS for the purpose of HIV prevention and care,[56] and can also identify those who are HIV negative, who can then be prioritised for prevention interventions to help them to maintain their status (eg, pre-exposure prophylaxis, VMMC). This approach, whereby HIV testing is central to the prevention–treatment continuum, moves away from general risk reduction messages for all audiences (eg, condom use, sexually transmitted infection [STI] treatment) towards specifically tailored approaches for individuals based on their serostatus and prevention needs.

Although HIV testing—which has historically been combined with risk reduction counselling—can prevent inadvertent transmission to sexual and needle-sharing partners in people living with HIV/AIDS, this effect is generally not noted in individuals who are HIV negative[62,63] (although the community-level benefit of testing on prevention is being investigated in Project Accept[64]). Research is focused on streamlining the content of the testing process, particularly in response to the diminishing support for pre-test counselling, by moving assessments of individual risk and plans for risk reduction to post-test sessions.[65,66] Hence, we refer to HIV testing alone as part of a large programme of combination prevention, which is intentionally disaggregated from a broad approach to HIV testing and counselling.

Much of the substantial scale-up in HIV testing[67] has been attributable to worldwide recognition of the value of expanding testing from client-initiated testing (eg, voluntary counselling and testing) to routine testing,[65] which could normalise and destigmatise HIV testing.[68] Furthermore, such strategies are cost effective,[69] have individual clinical benefits (via earlier detection),[70] and could potentially greatly reduce new infections when coupled with early start of ART.[49] However, successful implementation of so-called test-and-treat strategies are

challenged by the difficulties of testing of large numbers of healthy people who are not attending health-care services, incomplete engagement in HIV care,[56] and inadequate technology to detect people with acute HIV infection who are the most infectious.[17]

The most crucial questions for HIV testing centre on identification of the best strategies to increase demand for and provision of testing services, in both individuals and couples. Overall coverage of testing is low—a median of 17% of women and 14% of men in the general epidemics in sub-Saharan Africa from 2005 to 2009 had ever been tested for HIV infection and knew their results.[71] Demand for HIV testing is a complex function of access to health care, perception of risk, fear, stigma, and the threat of violence.[72–74] Although onsite rapid testing and provider-initiated testing can overcome some of these obstacles, approaches to mitigate fear and the threat of violence (particularly for women) are being investigated. Similarly, models of service delivery to optimise uptake of testing and linkage to care and treatment, while protecting patient rights and confidentiality, are an active part of operations research. Home-based, door-to-door testing is a promising model,[64,75] as are structural interventions, such as economic incentives,[76] which can play an important enabling part. In this way, both supply-side and demand-side barriers as well as inefficiencies can be addressed to improve access to and delivery of this key entry point to HIV prevention services.

Prevention of mother-to-child transmission

WHO's four-pronged strategy[77] for PMTCT recommends: (1) primary HIV prevention in women of childbearing age; (2) prevention of unintended pregnancies in women with HIV infection; (3) prevention of HIV transmission from women with HIV to their infants via use of antiretroviral drugs; and (4) provision of treatment, care, and support to women with HIV and to their families. To date, most emphasis has been placed on the third prong (perhaps at the expense of the others)—the integrated cascade of services centred on antiretroviral drug use offered in antenatal, perinatal, and postnatal care that together can reduce the risk of mother-to-child transmission to less than 5% in breastfeeding populations and less than 2% in non-breastfeeding populations.[78,79] For maximum effect, pregnant women who are HIV positive should receive a series of interventions, including attending antenatal care; being offered, accepting, and receiving the results of a HIV test; and accepting and adhering to antiretroviral-drug prophylaxis for themselves and their exposed infant: the PMTCT cascade. Thus, the success of PMTCT programmes is highly sensitive to the cumulative impact of attrition of mother–infant pairs at each step. Only 15–30% of pairs in high-burden countries complete the cascade.[80]

In 2010, WHO revised the guidelines for PMTCT treatment in response to increased evidence about the improved effectiveness of combination antiretroviral regimens compared with monotherapy (eg, single-dose nevirapine). The new guidelines recommended that all eligible pregnant women with HIV (ie, CD4 cell count ≤350 cells per μL) receive lifelong antiretroviral therapy for their own health, and that HIV-positive women who are not eligible for this therapy and their exposed infants have one of two prophylactic combination regimens to prevent transmission from mother to child.[79,81] Furthermore, for the first time, antiretroviral drug prophylaxis was recommended during breastfeeding in settings where breastfeeding is the safest feeding option for infants.

Worldwide, progress has been made in scaling up PMTCT in resource-poor settings. About 370 000 children born to mothers with HIV infection were newly infected with HIV in 2009—a decrease of 24% from 2004.[52] Testing coverage of pregnant women also improved from 7% in 2005 to 26% in 2009, and 53% of HIV-positive women in low-income and middle-income countries received antiretroviral drugs to prevent mother-to-child transmission in 2009—an increase from 45% in 2008, and 15% in 2005.[67] However, a recent demographic model showed that even if new HIV infections in women of reproductive age were halved, the unmet need for contraception was eliminated, the new guidelines had 90% coverage, and the duration of breastfeeding was reduced to 12 months, the reduction in new infections in children and the rate of mother-to-child transmission would still fall short of UNAIDS' objectives by 2015.[78] Thus, focus on all four prongs of WHO's PMTCT strategy is essential.

Understanding women's fertility intentions and the expansion of family planning services to HIV-infected non-pregnant and pregnant women is important to address the second prong of WHO's PMTCT strategy. The provision of contraception to women with HIV who do not want to become pregnant can be more cost effective than the provision of PMTCT services.[82] In addition, stimulation of demand and strengthening of delivery of services are a major focus of research attention, with particular emphasis on prevention of leakage at every step in the cascade. Low use of antenatal-care services, poor provider knowledge, low coverage of HIV testing, and poor patient documentation and tracking systems have hindered translation of research findings into routine practice.[83] Of the 25 highest burden countries, only ten had moved from single-dose nevirapine to more effective combination regimens for PMTCT by 2009, although WHO has recommended this approach since 2004.[84] Furthermore, the emphasis on immunological monitoring to establish ART eligibility will need substantial scale-up of CD4 cell testing (in 2008, only 24% of pregnant women with HIV received a CD4 cell count[85]) and complementary implementation research to identify models of service delivery that minimise attrition in view of the added complexity of combination regimens and immunological monitoring.[86]

Male circumcision

In the past 3 years, further studies have confirmed that VMMC reduces risk of HIV acquisition in men.[87–89] By contrast, the question of the protective effect of VMMC

for women has been debated. Although the benefit to women of their male partner not acquiring HIV is obvious, whether voluntary male circumcision has benefit for the woman if her partner is already positive is unclear. Findings from one randomised controlled trial suggested no immediate benefit of VMMC in reduction of transmission from infected men to their female partners,[90] but an older observational study[91] and a recent prospective study[92] showed reductions of up to 46% in male-to-female transmission. These data have led to revised calculations of the potential population-level effect of VMMC, with estimates of infection reductions for men and women as high as 28% in Zimbabwe.[93] These potential benefits are amplified by reductions in the risk of acquisition and transmission of human papillomavirus, the precursor to cervical cancer, in men,[94–96] although research is conflicting about the effect of VMMC on acquisition of *Trichomonas vaginalis*.[97,98]

Since 2008, district-level scale-up efforts in Kenya[99] and Tanzania[100] have shown that VMMC can be delivered at a pace and scale consistent with reaching population-level effect. However, although ecological studies[101,102] of populations in which traditional male circumcision is common provide some evidence for population-level outcomes, no data are available for how great an effect this scale-up will have on the epidemic. Efforts will benefit from implementation research, such as how best to create demand, increase levels of HIV testing, and maximise adherence to the 6-week period of sexual abstinence after surgery. Research into non-surgical methods[103,104] will also provide valuable options in settings where surgical staff are scarce.

Although there are examples of rapid and intensive scale-up, the same has not happened in some high-burden regions and countries. In many countries, policy makers have been slow to support VMMC.[105,106] This reluctance may stem from perceptions that support is biased towards particular religious groups, that its advocation will lead to widespread behavioural disinhibition, and that rollout will strain already overburdened health systems.[105,107] Indeed, although rapid scale-up seems best accomplished by assembly of one-time teams of health-care staff,[99,100] elements of the health system that are weak in many low-resource countries are still heavily relied on, highlighting the need for task shifting and further innovation into issues related to supply-chain, transportation, and financing. These real and perceived barriers have slowed the rollout of VMMC, but indications such as dedicated funding within PEPFAR bilateral budgets show that support is growing.

Structural and behavioural interventions

Structural interventions

Structural interventions can reduce high-risk behaviours, STIs, and known mediators of risk, including gender inequality and intimate partner violence.[108–110] Recently, studies of cash transfer programmes have strengthened the hypothesis that economic instability and poverty drive risk behaviour in young women. A randomised trial in Malawi[111,112] showed that girls receiving a cash transfer (either unconditional or linked to school attendance) had a lower prevalence of HIV and HSV-2 infections than did controls (60% and 75% lower, respectively), because of delayed sexual debut, fewer and younger partners, less sexual activity, and reduced transactional sex. A randomised trial in Tanzania[113] linking cash transfers to remaining free of STIs suggested that men and women receiving incentives had a 25% lower incidence of infection than did controls. By contrast, another programme in Malawi[114] that paid men and women to maintain their HIV-negative status for 1 year, noted no effect, although size and timing of the incentive might have been limiting factors. The preliminary results of these studies suggest that financial security could affect sexual behaviour, and that the promotion of economic empowerment and sustainable livelihoods might be key to reduction of HIV risk.[115]

Legislative reforms, reducing stigma and discrimination, and enhancing social capital are important structural interventions for a range of populations, including sex workers, men who have sex with men, and injecting drug users.[3] A systematic review showed that policy-level support and empowerment strategies for sex workers can improve acceptability, adherence, and coverage of HIV-prevention programmes.[116] Similarly, modelling suggests that approaches designed to mitigate the harmful effects of drug use, such as needle and syringe exchange programmes, medication assisted treatment for substance misuse, and other interventions, could substantially curtail epidemics related to injecting-drug users, particularly when implemented alongside non-discriminatory laws and rights-based interventions.[117,118]

Further research is needed to guide replication and scale-up of promising programmes, and to document how different structural interventions affect patterns and pathways of risk. Although structural interventions are difficult to evaluate in randomised trials,[8] important methodological innovations and lessons are emerging with new support from donors.[3,119,120] Further research should explore key elements of economic interventions such as microfinance (leading to independence and more choice and control over sexual partners and behaviours), including the additional benefits of training or community mobilisation.[109,121] For cash transfer programmes, understanding which behaviours can be incentivised is important, as is the size, frequency, and conditionality of transfers.[122] Finally, the importance of structural interventions that address cultural norms, gender and economic inequalities, migrant labour, and other factors underlying individual behaviour (eg, concurrent partnerships) is a substantial area of exploration.

For more on **PEPFAR bilateral budgets** see http://www.pepfar.gov

Behavioural interventions

Coates and colleagues[4] concluded that behavioural strategies were essential, but not sufficient, components of comprehensive HIV prevention and that "behavioural

strategies themselves need to be combinations of approaches at multiple levels of influence". Although estimates have suggested a decreased incidence of HIV in 33 countries, along with reduced sexual-risk behaviour in young people,[52,123] weaknesses in the availability of both programme evaluation and behavioural and epidemiological data make causal attribution of these reductions to HIV prevention programming difficult. For example, in Zimbabwe, careful analysis has suggested that incidence declines with behaviour change,[7,8] but this finding contrasts with a randomised controlled trial of a multipronged prevention intervention in one region of Zimbabwe that failed to show an effect (potentially because of timing or insufficient power).[124]

In the generalised epidemics of southern Africa, much attention has focused on overlapping or concurrent partnerships; albeit with controversy.[125,126] Although there is no disagreement that multiple concurrent partnerships contribute to risk for HIV transmission, and thus should be subject to HIV prevention programming responses,[127] the normative hold of concurrency makes such partnerships difficult to address directly. Regional media campaigns in South Africa suggest some preliminary effects on some risk behaviours, but no effects (as yet) for multiple partnerships.[128]

Behavioural strategies for prevention in men who have sex with men have shifted from generic strategies to ones that are tailored toward the serostatus of both partners. A review noted increased incidence in men who have sex with men in many high-income countries, and the prevalence of seroadaptive behaviours in these populations.[129] 14–44% of HIV-positive men who have sex with men, and 25–38% of those who are HIV negative, reported restricting unprotected anal intercourse to seroconcordant partners, and 14–35% and 6–15% of men who are HIV positive or negative, respectively, who have sex with men reported selecting insertive or receptive sex on the basis of HIV status. Evidence is available that men who have sex with men use partner viral load as another determinant in behaviours to reduce risk,[130] with added attention to this strategy after the so-called Swiss statement that HIV transmission in the context of fully suppressed viral load and absence of STIs was unlikely.[131]

See Online for webappendix

	Effectiveness of prevention intervention			Number of trials
	Positive effect	Adverse effect	No effect	
Behavioural	..	..	7	7
Structural: microfinance, CCTs	1*[111]	..	2[108,114]	3
Diaphragm use	..	..	1	1
Topical agents (microbicides)				
Non-ARV based	..	1	11	12
ARV-based PrEP	1[35]	..	..	1
Systemic, oral PrEP	1[39]	..	2†[133],‡[40]	3
Treatment as prevention	1[47]	..	..	1
Male circumcision	3	..	1	4
STI treament	1	..	8	9
Vaccine	1	..	3	4
Total trials	9	1	35	45

Results of 43 phase 2b or phase 3 randomised trials of 45 interventions to prevent the sexual transmission of HIV. Adapted from Padian and colleagues,[5] and updated with results of six trials since July, 2010 (the period since the last review).[35,39,40,47,111,114] See webappendix for full list of references for each category. Positive effect was when the intervention significantly reduced the risk of HIV in the intervention group compared with the control group; adverse effect was when the intervention significantly increased the risk of HIV in the intervention group compared with the control group; and no effect was when the intervention showed no significant effect (positive or adverse), thus the null hypothesis could not be rejected. CCT=conditional cash transfer. ARV=antiretroviral. PrEP=pre-exposure prophylaxis. STI=sexually transmitted infection. *Study, which has not yet been published in peer-reviewed publications, did not measure HIV incidence but showed differences in HIV prevalence. †Premature closure of the trial substantially reduced study power. ‡FEM-PrEP study prematurely closed because of futility after interim analyses revealed no protection against HIV. Table reproduced with permission from Wolters Kluwer Health.

Table: **Interventions to prevent the sexual transmission of HIV**

Behavioural prevention for injecting-drug users continues to focus on strategies aimed at mitigating the harmful impacts of drug use, in order to reduce risk behaviour (needle sharing) and HIV incidence.[117,132] Importantly, most studies have noted that the effect of these programmes is greatly enhanced with combinations of structural (eg, law reform), biomedical (eg, ART), and behavioural (eg, needle and syringe programmes) approaches.[117]

Difficulties in measurement of HIV incidence, together with the well documented problems in self-report of sexual behaviour, mean that the "gold standard" of evidence for behavioural interventions is unlikely to be reached soon.[5] However, large-scale behavioural change is clearly central to reduction of incidence, and behavioural interventions are crucial in amplification and facilitation of other prevention approaches, including driving demand for HIV services such as HIV testing, VMMC, PMTCT, and treatment. Assessment of the effect that these programmes have on service uptake might be useful both alone and as a proxy for effect on HIV incidence. Key questions for implementation of behavioural interventions concern the challenge of bringing community-based programmes to scale while maintaining quality and a better appreciation of the balance between local adaptability and fidelity.

Discussion

In the past year, HIV prevention has changed substantially and several efficacious interventions have reinvigorated the preventive science community (table). The value of prevention with antiretroviral drugs for individuals with and without HIV has emphasised the overlap of treatment and prevention, and reinforces the need for integrated strategies for epidemic control. No longer is it acceptable to consider expenditures for treatment and prevention separately; the challenges of sustainably financing epidemic control apply equally to both.[134] New prevention approaches demand increased interdisciplinary approaches within the prevention community. 30 years into the HIV/AIDS epidemic, clearly the separation of biomedical and behavioural prevention is outdated and inefficient. For example, the successes of biomedical interventions, such as pre-exposure prophylaxis and treatment for prevention, will rely as much on the ability

of an intervention to enhance adherence (behavioural), as on the drugs' pharmacokinetics (biomedical).

A significant change in new prevention findings is the promise for more prevention strategies whose initiation and implementation is under the control of women. For example, topical pre-exposure prophylaxis, especially when used as prophylaxis by women, has the potential to change the gender dynamic in the epidemic enormously. A vaccine would be the great equaliser, presumably protecting men and women indistinguishably. Additionally, growing research has shown that structural interventions including conditional cash transfers have the potential to reduce risk behaviours as well as STIs and HIV. Given that HIV in much of Africa disproportionately affects women,[52] this is a significant change in approach and holds substantial promise for future implementation. Until recently, all available prevention technologies, such as male and female condoms and male circumcision, required male initiation or acceptance, or both.

The central role of prevention based on antiretroviral drugs has emphasised the importance of adherence-independent approaches. Perhaps more importantly, the promise of such prevention has indicated that ethical and policy issues are as important as research into effectiveness. In view of scarce resources, the need to prioritise those who get antiretroviral drugs (pre-exposure prophylaxis or treatment for prevention), and consider the burden of distribution in view of frail health systems, calls for a different type of research that focuses on the balance between efficiency and equity and issues related to implementation science. An essential question is how a country's health service could maintain antiretroviral therapy in legions of healthy patients with high CD4 cell counts mainly for prevention benefits to partners, when it is not able to initiate and maintain high retention of those with low CD4 cell counts who need ART for survival.

HIV testing, VMMC, and PMTCT research should focus on implementation science issues related to efficient and effective scale-up, including methods to increase demand, uptake, and adherence, and those to optimise and strengthen elements of the health system, including procurement, supply chain, transportation, and sustained financing.

As we move forward, we cannot fail to assess impact.[135] Although methodological challenges such as the absence of a reliable incidence assay, the lack of naive control groups, and no suitable surrogates for HIV complicate evaluation, the time has come to require that programmes be implemented so that impact can be assessed. Concurrent advances in methods of evaluation have been made to support this effort.[136] This is essential in order to ensure transparent and unequivocal results that can demonstrate the effect of the programme being evaluated and just as importantly, that can inform the global effort to combat HIV/AIDS.

The future of HIV prevention is in operationalisation, implementation, and assessment of combination prevention programmes.[1,137] However, combination interventions have their challenges, including adaptation and replication of complex and multifaceted prevention programmes whose successes might depend on subtle factors of context or programme delivery. For example, the development of one integrative package that sufficiently incorporates local ownership of AIDS responses is unlikely; specifically, the need to tailor the combination to local epidemiology remains paramount. Our challenge is to carefully select a group of effective interventions that together have an increased chance of success by complementing each other to achieve the elusive goal of changing the course of the HIV epidemic.

Contributors

NSP, NH, BS, and SIM constructed the original outline of the manuscript. All authors participated equally to writing, revising, and the final approval.

Conflicts of interest

We declare that we have no conflicts of interest. The findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the US Department of State.

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