HIV Prevention 2

Biomedical interventions to prevent HIV infection: evidence, challenges, and way forward

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Intensive research efforts for more than two decades have not yet resulted in an HIV vaccine of even moderate effectiveness. However, some progress has been made with other biomedical interventions, albeit on the basis of inconsistent levels of evidence. The male condom, if used correctly and consistently, has been proven in observational studies to be very effective in blocking HIV transmission during sexual intercourse; and, in three randomised trials, male circumcision was protective against HIV acquisition among men. Treatment of sexually transmitted infections, a public health intervention in its own right, has had mixed results, depending in part on the epidemic context in which the approach was assessed. Finally, oral and topical antiretroviral compounds are being assessed for their role in reduction of HIV transmission during sexual intercourse. Research on biomedical interventions poses formidable challenges. Difficulties with product adherence and the possibility of sexual disinhibition are important concerns. Biomedical interventions will need to be part of an integrative package that includes biomedical, behavioural, and structural interventions. Assessment of such multicomponent approaches with moderate effects is difficult. Issues to be considered include the nature of control groups and the effect of adherence on the true effectiveness of the intervention.

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Historical overview

Before the discovery of HIV as the causative agent of AIDS, data from epidemiological studies suggested that the infectious agent was transmitted mainly through sexual intercourse.[1,2] On the basis of this evidence, public health authorities and advocacy organisations for men who have sex with men in industrialised countries issued recommendations for sexual behaviour change, including the use of the male condom for prevention of AIDS, as for other sexually transmitted infections.[3,4]

Observational studies of HIV-discordant couples provided initial evidence of the effectiveness of the male condom in prevention of HIV infection.[5] One of the early success stories was the increased use of condoms in high-risk locations, such as bath houses in the USA and brothels in Thailand; increased use of male condoms had a measurable effect on reduction of HIV transmission in these contexts.[6–8] Simultaneously, HIV was seen to be spreading at a devastating pace in sub-Saharan Africa and the primary means of transmission was through heterosexual intercourse.[9] Changes in sexual behaviour that had occurred in selected communities at risk of HIV infection were too small and too slow to bring this new epidemic quickly

Key messages

- No HIV vaccine or topical prophylaxis will be available in the foreseeable future. Thus far, the only biomedical interventions that are effective in prevention include use of male condoms; male circumcision; and prophylactic use of antiretroviral drugs or contraception to prevent unwanted pregnancies to reduce mother-to-child transmission. Oral and vaginal antiretroviral drugs both for pre-exposure prophylaxis and to reduce infectiousness among HIV-positive individuals are being assessed. Treatment of sexually transmitted infections, a strong public health intervention in its own right, has had mixed results in trials in which the effect on prevention of HIV acquisition was assessed
- The prophylactic use of antiretroviral drugs in sexual transmission of HIV, both orally and vaginally, shows great promise. Here (as with sexually transmitted infection treatment to prevent HIV), research should focus on reduction of infectiousness to prevent transmission and thus should target infected individuals. Should these strategies prove effective, issues related to resistance and distribution will have to be considered before scale-up
- Challenges for assessment of multicomponent interventions, especially those postulated to have modest effects, include the ability to distinguish the marginal effect of the new intervention over that of an intensive prevention package, the nature of the control group, and separation of the effect of adherence (potentially modifiable) from the potential of the intervention
- Biomedical interventions should be integrated with other modes of prevention. These combination prevention strategies are needed to maintain adherence, to avoid sexual disinhibition (risk compensation), and are essential for addressing mechanisms that are necessary for scale up to optimise effects
- Presently, we apply different levels of evidence, depending on the intervention (eg, male condoms *vs* male circumcision). To scale up effective interventions, the level of evidence needed requires more than biological effectiveness of the intervention; operational considerations, such a long-term adherence, the possibility of harm, and sustainability have to be considered

Search strategy and selection criteria

We searched Medline, PubMed, and the Cochrane Library for papers published in peer-reviewed journals during the past 10 years, and identified conference abstracts from the past year from relevant conference websites and the US National Library of Medicine Gateway up to the end of April, 2008. The review was not necessarily systematic because the authors were already aware of many of the articles cited. The search was not restricted by language. Search terms included "HIV", "prevention", "male condoms", "female condoms", diaphragms", "cervical barriers", "sexually transmitted infections", "sexually transmitted diseases", "HSV-2", "male circumcision", "microbiocides", "mother-to-child transmission", "antiretrovirals", and "vaccines". We focused largely on identification of randomised controlled trials; however, rigorously done observational cohort studies were included to fill gaps in the data. Additionally, we reviewed relevant publications and website materials from international organisations , such as UNAIDS and WHO, and non-governmental organisations and advocacy groups involved in biomedical HIV prevention research. References were updated on the basis of suggestions from our reviewers and other experts in the specialty and as needed to include the most up to date publications.

under control.[10] Thus, the search for a quick technological, biomedical fix that did not rely on behaviour began in earnest.

The isolation of HIV in 1983 opened up the possibility that the spread of the virus could be controlled with a vaccine. The development of an effective vaccine against another related virus—ie, feline leukaemia virus—raised hopes that an AIDS vaccine was within reach.[11,12] However, this optimism did not last long when the extent of the genetic diversity of HIV was revealed.[12] Despite major advances in our understanding of the virology and immunology of this virus during the past two decades, little progress in HIV vaccine development has resulted. Even now, most experts predict that no vaccine will be available for at least another 20 years.[11,13]

Several potentially modifiable risk factors for HIV transmission, such as curable sexually transmitted infections and male circumcision were identified in epidemiological studies.[14,15] Control of sexually transmitted infections through prompt diagnosis and treatment soon became a focus for prevention of HIV transmission. HIV incidence was successfully reduced in the first such trial, done in Tanzania.[16] However, these results were not reproduced in three similar trials, and the place of sexually transmitted infection control in reduction of the transmission of HIV remains to be settled. [17–19]

By contrast, results of three separate randomised trials showed the uniform and unequivocal protective effect of male circumcision in reduction of HIV acquisition.[20–22] The evidence from these trials prompted WHO and UNAIDS in 2007 to recommend male circumcision for the prevention of HIV transmission in populations seriously affected by HIV.[23]

Although the effectiveness of the male condom in blocking HIV transmission was never in question, widespread promotion of male condoms ignored the need for female-initiated prevention methods.[24] In areas of the world most greatly affected by HIV, women and young girls account for most of those infected.[25] Sociocultural, economic, and gender-inequity differentials contribute to the high incidence of HIV infection among women by restricting their ability to negotiate the use of male condoms.[26–28] Female-initiated methods, including physical barriers and topical antimicrobial (microbicide) products, would need to be easy to use, cheap, non-toxic, and effective in prevention of HIV transmission during sexual intercourse.[24] Several products that meet these criteria have been tested in phase III trials but were ineffective or even harmful.[29–35]

The focus on chemical barriers has now shifted from easy to use and cheap over-the-counter products to formulations containing antiretroviral drugs. At the same time the systemic use of antiretroviral drugs is also being tested as pre-exposure prophylaxis. Optimism for this prophylactic approach is based partly on the use of antiretroviral drugs in the prevention of HIV transmission from mother to child, first tested in the early 1990s, and after needle-stick injury in the health-care setting.[36,37] With the exception of male condoms and circumcision, all biomedical prevention methods in development are as equally controlled by women as by men (table 1).

In this review, we discuss the state of biomedical HIV prevention research (table 2), focusing on sexual transmission and classified by the specific mechanism of action rather than the mode of delivery. We review physical barrier methods; control of other sexually transmitted infections; male circumcision; topical antimicrobial (microbicide) preparations; the prophylactic use of antiretroviral drugs (oral and topical); and HIV vaccines.

For each of these prevention methods, we describe the available evidence for efficacy or effectiveness, make recommendations for their use, and suggest future needed research. We will also review levels of evidence for effectiveness for each method, the common challenges for HIV biomedical research, and suggest a way forward.

Physical barrier methods

Male condoms

Since the early 1980s, when use of male condoms was first recommended to prevent HIV transmission, evidence of the effectiveness of this approach has been accumulating.[39–44] In-vitro tests for virus penetration of latex (the most widely available) and polyurethane condoms showed that intact condoms are essentially

impenetrable to particles the size of sexually transmitted pathogens.[45] A Cochrane review estimated the effectiveness of male latex condoms for prevention of HIV transmission as 85%, on the basis of data from several longitudinal cohort studies of serodiscordant heterosexual couples.[40] When male condoms are used consistently, their effectiveness can be as high as 95%.[46] However, the effectiveness of condoms at the population level is not well established. In many populations, the male condom is not well accepted even as a contraceptive device. For example, although individuals might use condoms successfully with particular partners (eg, clients of sex workers), their use with regular or steady partners might be suboptimum.[47–49] Another challenge is that, as opposed to contraception for which the risk of pregnancy varies during the course of the menstrual cycle, protection against infection requires consistent use of the male condom. Condoms have to be available immediately for coital use, and thus a continuous source of supply is needed.

Despite these challenges, vigorous and creative condom promotion campaigns and marketing of various condoms have brought some changes in perception and uptake of condoms. Analyses of data from the Demographic and Health Surveys have shown increases in the use of condoms by young, unmarried women in Latin America and sub-Saharan Africa.[50,51]

Female condoms

Use of male condoms depends on the willingness of men to use them. This obstacle led to the design of the female condom, which is so far the only female-initiated biomedical method available for prevention of HIV transmission. The female condom provides a physical barrier that prevents exposure to genital secretions containing HIV, such as semen and vaginal fluid. Like their male counterparts, laboratory tests have shown that polyurethane female condoms also provide an effective physical barrier against HIV transmission.[52] The effects of the female condom on semen exposure[53] and sexually transmitted infection rates have been assessed in several clinical trials;[54–56] however, the ability of the female condom to prevent HIV infection has not been directly assessed. In a crossover trial in which male and female condoms were compared, increased rates of semen exposure (detected by postcoital prostate-specific antigen test) and self-reported mechanical difficulties were noted, which might suggest lower effectiveness of female condoms for prevention of transmission.[53] By contrast, in a randomised controlled trial that compared women who were provided with condom counselling and male condoms with those who were provided with condom counselling and female condoms, rates of sexually transmitted infections (gonorrhoea, chlamydia, syphilis, and trichomoniasis) did not differ substantially, suggesting that male and female condoms have similar effectiveness.[54]

Uptake of the female condom has been less than ideal. The conspicuous presence of the device and its high cost have prevented widespread acceptance of this promising prevention intervention.[57–59] New designs that

Adherence	Intervention	Level of evidence	Effectiveness	Female controlled
Single decision	Male circumcision	Level I/RCTs	Effective for preventing acquisition	No
Several decisions	Vaccine	Level I/RCTs	Ineffective for preventing acquisition. Possible harm	Yes
Daily decisions	STI/HSV suppression	Level I/RCTs	Not known	Yes
	Oral antiretroviral drugs	None	None	Yes
	Topical antiretroviral drugs	None	None	Yes
Coitally related decisions	Male condom	Level II-1/ cohort studies	Effective	No
	Diaphragm	Level I/RCT	Ineffective in provision of additional protection *vs* condoms and STI treatment	Yes
	Topical surfactants, entry/fusion inhibitors	Level I/RCTs	Ineffective in prevention of acquisition. Possible harm	Yes

HSV=herpes simplex virus. RCTs=randomised controlled trials. STI=sexually transmitted infection.

Table 1: **Biomedical interventions for HIV prevention**

	Population and study product	Number of participants	Study sites	Expected results (year)
Herpes simplex virus-2 suppression				
Partners in Prevention trial (NCT00194519)	HIV-1 discordant couples; aciclovir	3400*	Kenya, Tanzania, South Africa, Uganda, Rwanda, Zambia, Botswana	2008/2009
Topical antimicrobial preparations				
HPTN 035 trial (NCT00074425)	Women; BufferGel and 0·5% PRO2000 gel	3220	Malawi, South Africa, USA, Zambia, Zimbabwe	2009
MDP trial (NCT00262106)	Women; 0·5% PRO 2000 gel†	9580	South Africa, Tanzania, Uganda, Zambia	2009
Antiretroviral drugs for prevention				
Oral				
CDC trial (NCT00119106)	Male and female IDUs; tenofovir	2400	Thailand	2008
CDC trial (NCT00448669)	Heterosexual men and women; Truvada‡	1200	Botswana	2010
iPrEX study (NCT00458393)	MSM; Truvada‡	3000	Ecuador, Peru, US, Africa, Asia	2010
Topical				
CAPRISA 004 trial (NCT00441298)	Women; 1% tenofovir gel	980	South Africa	2010
Vaccines				
Prime and boost trial (NCT00476749)	Men and women; primed with ALVAC-HIV vCP1521; boosted with glycoprotein 120	16 000	Thailand	2009

HPTN=HIV Prevention Trials Network. MDP=Microbicide Development Programmes. CDC=Centers for Disease Control and Prevention. IDUs=injecting drug users. MSM=men who have sex with men. CAPRISA=Centre for the AIDS Programme of Research in South Africa. *Couples. †On Feb 11, 2008, after a review of the data by the Independent Data Monitoring Committee for the MDP recruitment to the 2% PRO 2000 group of the trial was halted owing to futility.[38] ‡Proprietary name for emtricitabine and tenofovir disoproxil fumarate.

Table 2: **Ongoing efficacy trials for biomedical prevention of HIV transmission**

	Candidates*	
Surfactants		
Disable the virus by breaking up the membrane surface	Savvy (C31G)	Two phase III trials were halted early because HIV incidence was lower than expected
Vaginal defence enhancer		
Maintains normal microflora and acidity of the vaginal environment	BufferGel	Phase IIB in progress
Entry/fusion inhibitor		
Prevents attachment to and entry of virus into target cells	Carraguard (PC-515)	Phase III completed; safe, but not effective in prevention of HIV infection
	UsherCell (cellulose sulphate)	Two phase III trials were stopped; the DSMB for one trial reported a higher number of HIV infections in the treatment group than in placebo group
	2% PRO 2000	This arm of a phase III trial was stopped because of futility
	0·5% PRO 2000	Phase IIB and III in progress
	VivaGel (SPL 7013)	Phase I in progress
	Invisible Condom	Planned phase III assessment
Viral replication inhibitor		
Suppresses replication of HIV that enters the vagina or rectum during intercourse	Tenofovir	Phase IIB in progress
	Dapivirine	Phase I in progress
	UC-781	Phase I in progress

DSMB=data and safety monitoring board. *Includes products being assessed in human beings and products that have completed phase IIB/III trials within the past 2 years.

Table 3: **Mechanisms of action for topical antimicrobial and antiretroviral preparations**

reduce the cost, are easier to use and reuse, and are better able to transmit heat and sensation, might increase uptake.[60–62]

Cervical barriers

Though originally developed as contraceptive devices, cervical barriers such as the diaphragm might be protective against HIV acquisition.[63–65] The effect of a cervical barrier in prevention of HIV transmission has been examined in only one trial. In the MIRA (Methods for Improving Reproductive Health in Africa) trial,[66] the effect of a diaphragm plus polycarbophil (Replens) lubricant on acquisition of HIV was examined. The authors reported no additional protective effect of latex diaphragm, lubricant gel, and condoms compared with condoms alone.[66] Adherence to the use of the diaphragm was lower than expected. Additionally, condom use differed by group, with less use by diaphragm users. This difference might have signalled increased risk if diaphragms had been less effective than condoms; however, infection rates were statistically indistinguishable between the groups. Similar infection rates might suggest that the diaphragm compensated for unprotected sex among women who did not use condoms, and that diaphragms are therefore as effective as condoms, or simply that women in the condom group were more likely to report condom use than those in the diaphragm group.

Despite these uncertainties, diaphragms could continue to have an important role in HIV prevention as a mechanism for topical delivery of antimicrobial and antiretroviral products.[66] For example, if safe and effective against HIV, BufferGel, a non-specific topical antimicrobial gel (table 3) will be combined with a disposable, one-size-fits-all, clear diaphragm made of polyurethane (BufferGel Duet). This cervical barrier and antimicrobial combination could be more effective than the antimicrobial product alone. The ability of the BufferGel and diaphragm combination to prevent pregnancy has already been tested and was reported to effectively prevent pregnancy.[67,68] The question remains as to whether diaphragms are as protective as condoms, which could have enormous public health importance for women whose partners are unable or unwilling to use male condoms and who find female condoms too conspicuous.

Control of other sexually transmitted infections to prevent HIV infection

The sexual transmission of HIV infection within partnerships seems to be facilitated by several sexually transmitted infections.[69,70] Longitudinal epidemiological studies have provided direct evidence that sexually transmitted infections in HIV-uninfected men and women increases their susceptibility to HIV infection, with genital ulcerative diseases, such as syphilis, chancroid, and genital herpes having larger effects on susceptibility than gonorrhoea, chlamydial infection, and trichomoniasis in women.[70,71] Evidence for increased infectiousness associated with sexually transmitted infections comes from studies in which shedding of HIV in genital secretions was compared before and after treatment of a concurrent sexually transmitted infection.[72–74]

Interventions for curable sexually transmitted infections

Since the early 1990s, four community randomised trials have assessed the effect of interventions specifically designed to control the most common curable sexually transmitted infections (chancroid, syphilis, gonorrhoea, chlamydial infection, and trichomoniasis) on HIV incidence.[16–19] In Mwanza, Tanzania;[16] Masaka, Uganda;[17] and Manicaland, Zimbabwe,[18] the intervention consisted of improved case detection and treatment of symptomatic sexually transmitted infections in primary health-care services. The intervention tested in Rakai, Uganda[19] included periodic mass treatment of sexually transmitted infections. Although a significant reduction in HIV incidence was reported in those communities receiving improved case detection and treatment of sexually transmitted infections in the Mwanza trial, no effect of the sexually transmitted infection intervention on HIV incidence was reported in the other three trials. The most plausible explanation for the differences in effect between

the trial in Mwanza and the two trials in Uganda is that the epidemic in Uganda was more established than that in Mwanza, with lower risk behaviour and lower rates of curable sexually transmitted infections.[75] The implication is that the effect of treatment services for curable sexually transmitted infections depends on the stage of the epidemic and decreases with time as the HIV epidemic becomes established.

Herpes simplex virus type-2 (HSV-2) infection and spread of HIV

In a meta-analysis of the effect of HSV-2 infection on HIV acquisition, prevalent HSV-2 infection was associated with a three-fold greater risk of heterosexually acquired HIV infection in the general population.[76] In sub-Saharan Africa, 38–60% of new HIV infections in women and 8–49% of incident infections in men could be attributable to HSV-2 infection. Furthermore, in epidemiological modelling studies that used empirical data from sub-Saharan Africa, the attributable fraction of new HIV infections associated with curable sexually transmitted infections decreased with time, whereas that attributable to HSV-2 increased.[77,78]

Two trials have assessed the effects of aciclovir treatment on the risk of HIV acquisition in HSV-2-infected women and men who have sex with men.[79,80] Overall, no evidence of a protective effect was noted, although in one trial some protection was noted in women who took at least 90% of the prescribed doses.[79]

Indirect evidence that HSV-2 infection increases infectiousness of HIV in co-infected individuals is provided by studies of genital HIV shedding.[81] Two randomised trials on the effects of suppressive treatment with valaciclovir on HIV shedding in co-infected individuals have so far been reported.[82,83] In both trials, valaciclovir treatment was associated with reduced shedding of HIV in genital secretions, suggesting that HSV-2 suppressive treatment of co-infected individuals might reduce HIV transmission.[82,83] Proof that this is indeed the case will be provided by the results of the Partners in Prevention trial (table 2) in which individuals co-infected with HIV and HSV-2 receive aciclovir to reduce HIV transmission to their uninfected partners. Results are expected in 2008 or 2009.

Interventions to control HSV-2 infection by suppressive treatment with aciclovir or valaciclovir require high levels of adherence; introduction of such interventions at a population level is probably not feasible, especially since the prevalence of HSV-2 infection is high in many low-resource settings.[84] Moreover, no convincing evidence has yet been reported that HSV-2 suppression will have an effect on HIV transmission. Further research is urgently needed to elucidate the determinants of immunity against HSV-2 infection and to develop an HSV-2 vaccine that is more effective than the presently available gD2-Alum MPL vaccine.[85,86]

Sexually transmitted infection treatment programmes might also have an effect on HIV transmission that goes beyond the biological effect of treatment on virus transmission. These programmes offer unique opportunities to reach high-risk men and women with counselling and other interventions for prevention of HIV transmission.

Male circumcision as a prevention strategy

An estimated 30–34% of adult men worldwide are circumcised. Male circumcision is practised for religious, cultural, and medical reasons, and the proportion of men who are circumcised varies between populations from less than 5% to more than 80%.[23] For some time, researchers have speculated that male circumcision might reduce HIV acquisition in men. The inner surface of the foreskin has a high concentration of HIV target cells. It is lightly keratinised and susceptible to microscopic tears, is exposed to vaginal secretions during sexual intercourse, and provides a moist environment that might sustain the viability of pathogens.[22,87–91] Furthermore, uncircumcised men have higher rates than circumcised men of genital ulcer disease, which is also associated with HIV transmission.[92,93] Thus, presence of the foreskin might facilitate survival and entry of the virus.

Evidence from randomised controlled trials

Evidence from observational studies strongly supported an association between male circumcision and HIV infection.[93–98] Three randomised trials were therefore initiated to assess the effect of male circumcision on HIV acquisition in men. The trials were done in healthy men in South Africa, Kenya, and Uganda. All three trials were halted early by their respective data and safety monitoring boards.[20–22] The summary rate ratio for the three trials was 0·42 (95% CI 0·31–0·57), identical to that obtained from observational studies,[99] which translates into a protective effect of male circumcision of 58%. The trials also assessed whether male circumcision could lead to sexual disinhibition because men might believe that they were protected against HIV infection after circumcision. In Kenya and Uganda, no evidence for an increase in risky sexual behaviour was reported,[21,22] whereas in South Africa circumcised men reported significantly greater numbers of sexual partners per month than did those in the control group 21 months after the intervention.[20]

Observational studies also suggested that male circumcision might reduce HIV transmission from infected men to their female partners.[94] However, in a study in Uganda, circumcision of HIV-infected men did not result in any protective effect against HIV transmission to female partners.[100] That study further suggested that early resumption of sexual intercourse, before complete wound healing, might increase the risk of male-to-female HIV transmission. Since exclusion of HIV-infected men from circumcision programmes might

not be possible, these findings underscore the need for intensive counselling of participants about abstention from sexual intercourse until healing is complete, and adherence to other risk-reduction behaviours. However, male circumcision might reduce HIV infection rates in women indirectly through reduction of the prevalence in male partners over time.

Historically, observational studies of circumcision effects on HIV transmission in men who had sex with men have had inconsistent results,[101–103] partly because of role versatility, wherein men adopt both insertive and receptive sexual roles. HIV acquisition is more likely with receptive anal intercourse than with insertive anal intercourse.[104] In a cohort study[105] of HIV-negative men who have sex with men, no association between circumcision and HIV seroconversion was reported, even after adjustment for behavioural factors and the presence of anorectal sexually transmitted diseases. The evidence thus far suggests that male circumcision is a less effective method of prevention of HIV transmission for men who have sex with men than for men who have sex with women.

On the basis of the findings from the three clinical trials, a WHO and UNAIDS consultation in March, 2007, recommended that circumcision should be recognised as an effective intervention for HIV prevention of heterosexual HIV acquisition in men.[106] WHO and UNAIDS also recommended that male circumcision be offered to HIV-negative men in addition, but not as a substitute, to other HIV risk-reduction strategies. The public-health effect of male circumcision will be largest in generalised epidemics. As such, WHO and UNAIDS recommend that countries with hyperendemic and generalised HIV epidemics and low prevalence of male circumcision expand access to safe male circumcision services within the context of ensuring universal access to comprehensive HIV prevention, treatment, care, and support.[106] Male circumcision is a one-time procedure, which is not coitally dependent, and is therefore likely to be a cost-effective method for prevention of HIV transmission. Kahn and colleagues[107] have estimated that in Gauteng Province, South Africa (where HIV incidence is 3·8 per 100-person years), the cost per HIV infection averted might be as low as US$181, based on a cost of $47 per procedure. A 100% uptake of male circumcision could avert an estimated 2 million new infections and 0·3 million deaths during 10 years in sub-Saharan Africa and 5·7 million infections during 20 years.[108]

However, male circumcision as a HIV prevention strategy has many challenges. Several studies have assessed the acceptability of male circumcision in populations that do not traditionally practice this procedure.[109] High levels of acceptability in these populations were reported in the studies, but once the programmes are scaled up, their uptake remains to be seen. Despite the encouraging trial results, valid concerns remain about the possibility that male circumcision could lead to increases in high-risk sexual behaviour. Epidemiological modelling suggests that an increase in risky sexual behaviour after circumcision could potentially offset beneficial effects of circumcision if not prevented by means of appropriate health education, including HIV testing.[110] Promotion of male circumcision should thus be accompanied by clear messages about its effects and the continued need for adherence to safe sex practices. Perceptions about the effects of male circumcision and any changes in sexual behaviour at the population level should be carefully monitored.

Unsterile cultural circumcision done as part of adolescent coming-of-age ceremonies undermines the safety of the procedure and is associated with increased rates of surgical complications.[111,112] In some countries in west Africa (eg, Mali) where male circumcision is traditionally done before the age of sexual debut, most parents now choose to use health facilities for medical circumcision because of safety and cost (Hankins C, UNAIDS, Switzerland, personal communication). Other countries such as Swaziland, Rwanda, and Kenya are developing plans for country-wide scale-up. Circumcision done before adolescence, particularly in early infancy, has the advantage of being technically easier and ensures that wound healing is fully complete before the initiation of sexual activity. Substitution of surgically safe circumcision procedures for unsafe, unsterile traditional practices is essential.

Antimicrobial products for HIV prevention

The term microbicide was coined to define a range of chemical products such as gels, creams, films, or suppositories that might prevent HIV transmission when inserted into the vagina or rectum before sexual intercourse.[113] This concept was initially conceived of as a female-controlled method (vaginal application) to prevent sexual transmission via heterosexual intercourse; however, safe and effective antimicrobial compounds could also serve as important prevention methods for men who have sex with men (rectal application).

The first trials focused on nonoxynol-9 which had a half-century track record of being used safely as a spermicide. Moreover nonoxynol-9 gel seemed to be effective against HIV in vitro and was available over the counter. In the 1980s, observational data for nonoxynol-9 gel against sexually transmitted infections, including HIV infection, were encouraging. However, in randomised trials in the 1990s, this gel was ineffective in prevention of HIV infection and other sexually transmitted infections.[30,34,114]

These trials were followed by studies to assess other non-HIV-specific agents, such as vaginal defence enhancers, surfactants, and entry and fusion inhibitors (table 3). Several of these products, including 1% C31G, 6% cellulose sulphate, 2% PRO 2000, and PC-515 have been assessed in phase IIB and III trials, all with disappointing results (table 3).[29,31–33,35,38] Other candidate antimicrobial products are being assessed (table 2).

At present, no antimicrobial products have been proven to protect against vaginal or rectal HIV acquisition. In response, research has moved in three new directions. First, new agents now include antiretroviral compounds that specifically inhibit HIV replication, which might hold more promise for prevention of HIV transmission than their non-specific counterparts. Second, formulation research is moving towards longacting dispersal methods and away from delivery mechanisms that are coitally dependent or require frequent application. Several trials are examining the safety and acceptability of a longacting vaginal ring as a product delivery system.[115–117] With easy insertion and the possibility of long-term release, the vaginal ring has the potential to be an effective delivery mechanism when combined with safe and effective antimicrobial or antiretroviral compounds.[118] Third, combination products composed of several different compounds with different mechanisms of action are undergoing preclinical assessment.

Antiretroviral prevention

The advent of antiretroviral therapy was a crucial turning point in the HIV/AIDS epidemic. Novel antiretroviral drugs have revolutionised the treatment of HIV/AIDS, adding decades to the lives of those infected. As the worldwide effort to expand access to antiretroviral treatment continues, researchers are also assessing antiretroviral compounds for their prevention potential in addition to treatment.

Oral antiretroviral prevention to reduce susceptibility

The first widespread use of antiretroviral drugs for prevention started in the 1990s with antiretroviral prophylaxis to prevent mother-to-child transmission of HIV. The use of short-course zidovudine and subsequently single-dose nevirapine for pregnant, HIV-infected women has been proven to reduce mother-to-child transmission in non-breastfeeding populations by two-thirds.[36,119] Several other regimens have been assessed in non-breastfeeding and breastfeeding populations during the past two decades. Antiretroviral prophylaxis has three effects: it reduces infectiousness by lowering the maternal viral load;[120,121] it provides pre-exposure prophylaxis to the infant;[122,123] and it provides post-exposure prophylaxis for the infant after birth.[124–130] In two completed studies, further reductions in HIV incidence in infants receiving extended antiretroviral regimens compared with single-dose or short-course regimens were reported.[131,132] Additional studies are in progress to assess the continuation of antiretroviral treatment to the breastfeeding mother.[133] WHO recommendations to prevent mother-to-child transmission involve a four-pronged strategy to prevent transmission (panel) that includes antiretroviral drugs for pregnant women and for infected mothers when HIV disease progresses.[140]

***Panel:* UN strategy for prevention of mother-to-child transmission**

The UN Interagency Task Team for mother-to-child transmission of HIV infection has proposed a four-component strategy to reduce mother-to-child transmission:

- Prevent HIV infection in all people, especially young women
- Prevent HIV transmission from HIV-infected women to their infants through antiretroviral treatment, safe delivery practices, and counselling and support for infant-feeding methods
- Provide care and support to HIV-infected women, their infants, and families[134]
- Prevent unintended pregnancies in HIV-infected women
  - Effective methods of contraception are safe for use[135]
  - Prevention could produce greater reductions in infant HIV incidence than the use of antiretroviral prophylaxis in pregnancy[136–138]
  - Access to effective contraception is restricted in many resource-poor countries
  - HIV voluntary counselling and testing programmes are often separate from those for reproductive health. Integration of HIV and reproductive health services could lead to reduction in unintended pregnancies in both HIV-infected and HIV-uninfected women[139]

A complementary, cost-effective strategy to reduce mother-to-child transmission is prevention of unintended pregnancy in HIV-infected women who do not wish to become pregnant.

On the basis of the success of antiretroviral drugs to prevent mother-to-child transmission, researchers are now assessing antiretroviral chemoprophylaxis for prevention of other means of transmission. Pre-exposure prophylaxis involves the provision of oral or topical antiretroviral drug to HIV-uninfected individuals before HIV exposure.[141] If proven safe and effective, this approach might be more user-friendly because it could be delivered independently of sexual practices and other risk behaviours, either daily or intermittently to coincide with planned sexual intercourse. Studies in non-human primates of pre-exposure prophylaxis have shown effectiveness; however, effectiveness has yet to be shown in people.[142,143] Several trials examining oral chemoprophylaxis in high-risk adults are in progress (table 2).

Topical antiretroviral preparations

After the disappointing results from trials of topical antimicrobial products, researchers turned to antiretroviral drugs that specifically target HIV and inhibit viral replication (table 3). These promising agents are being assessed separately, although the development of combination products with different anti-HIV mechanisms is also of interest. The combination could potentially be more effective than either product alone.[144]

With the viral specificity of these products, their application might be more readily expanded to include rectal and vaginal use by heterosexual couples and men who have sex with men. Although no product has been specifically developed for rectal use, several male tolerance and rectal safety studies of antiretroviral products, such as UC-781, are being done in parallel with vaginal safety trials.[117]

Antiretroviral treatment to reduce infectiousness

Antiretroviral therapy of individuals already infected with HIV is being assessed as a strategy to reduce infectiousness and thus reduce or prevent transmission. High plasma viral load is highly associated with increased infectiousness;[145–149] conversely, antiretroviral treatment reduces both plasma and genital viral load (in men and women).[150–153] On the basis of this evidence, antiretroviral treatment should plausibly reduce the infectiousness of those HIV-infected individuals who are not clinically indicated to be on antiretroviral drugs. Switzerland's Federal AIDS Commission concluded, on the basis of a review of four studies in which HIV transmission in serodiscordant couples was examined,[145,154–156] that seropositive individuals are not at risk of transmitting HIV to a seronegative partner when HIV has been undetectable in the blood of the seropositive partner for at least 6 months, the infected partner strictly adheres to his or her antiretroviral regimen, and he or she is free of any other sexually transmitted infections.[157] In one continuing study of HIV-1 serodiscordant couples (table 2), participants in the intervention group receive antiretroviral drugs earlier than clinically indicated (CD4+ cell count 350–550 cells per μL), whereas those in the control group receive antiretroviral treatment in accordance with standard WHO guidelines for treatment. This phase III, multicentre trial is presently enrolling couples and results are expected in 2012.[158]

If antiretroviral drugs show effectiveness when given prophylactically, research into prevention of HIV transmission would shift to questions about the best regimen, the most convenient form of dosing, and the most appropriate high-risk populations for the intervention. As the worldwide HIV/AIDS community awaits the results of these crucial trials, we need to consider issues related to the distribution and use of antiretroviral drugs for prevention, including viral resistance, long-term toxic effects or side-effects, the possibility of drug sharing or black markets in resource-constrained settings, and, more generally, the ethics of making antiretroviral drugs available for prevention in areas where treatment coverage might be insufficient.

Vaccines

In the past 25 years, the amount of effort and funding to develop a vaccine has grown substantially. Nevertheless, no HIV vaccine of even moderate effectiveness is yet available. In the past decade, a plethora of collaborations have been underwritten to focus on HIV vaccines.[159] Total investment in vaccine research in 2006 amounted to $933 million but the much-needed breakthrough has not yet happened. The scientific challenges are daunting; several leading scientists in the specialty doubt whether we will ever have a vaccine.[11]

Originally, vaccine research focused on identification of immunogens that would elicit neutralising antibodies at sufficiently high concentrations to prevent infection.[160] However, these efforts have been thwarted by the high genetic variability of the virus and its capacity to escape the effects of neutralising antibodies. Two phase III trials of a vaccine against glycoprotein 120, which aimed to elicit neutralising antibodies against the HIV-1 envelope, did not find any protection of healthy individuals against HIV infection.[161,162] Nevertheless, efforts to design vaccines that elicit protective antibody responses continue.

Studies of early infection in people and experiments on non-human primates have drawn attention to the importance of T-cell immunity in containing HIV infection.[160] Immunisation with a vaccine that stimulates T-cell responses might not be able to prevent infection with HIV, but might reduce the initial viral load after infection and the viral set point. Low initial viral loads have been associated with slower disease progression, and reductions in transmission of the virus.[163,164] The first T-cell vaccine tested in a phase IIB trial was the V520 vaccine, which consisted of a replication-defective adenovirus type-5 vector with three HIV genes. In September, 2007, after 3000 individuals had been enrolled, an interim analysis showed that the vaccine neither prevented HIV acquisition nor reduced the initial viral load despite induction of the T-cell response.[11,165] Even worse, more HIV infections occurred in study participants who had higher pre-existing levels of immunity against adenovirus type 5 and who had received the vaccine.[166] Trials of the T-cell vaccines are being examined for their future relevance.

One phase III HIV vaccine trial is in progress (table 2) to assess the vaccine strategy of prime and boost which primes the immune system with a live recombinant canary pox vector that contains HIV genes (ALVAC-HIV vCP1521), followed by a boost with vaccine against glycoprotein 120 (table 2). Results from this trial are expected in 2009.

Despite these disappointing results, HIV vaccine research will continue with a renewed basic science focus to gain an improved understanding of the immune responses to the virus.[167,168] Clinical data suggest that an HIV vaccine might be feasible. Some HIV-infected individuals seem to produce broadly neutralising antibodies that bind to most of the circulating HIV-1 strains; in non-human primates infusion of high doses of neutralising antibodies have been proven to protect against infection with primate lentiviruses.[169,170] Reported cases of women who do not become infected despite

repeated exposure to HIV-infected sex partners are encouraging.[171] In some HIV-infected individuals the infection seems to be controlled spontaneously; however, the mechanism remains largely unknown.[172]

What works: level of evidence

Surveillance shows that for every eligible individual put on treatment, another six people are newly infected.[25] Even though in many areas, prevalence seems to be decreasing,[25,173] the epidemic will never be controlled without effective prevention. Only one biomedical prevention intervention—male circumcision—has achieved level 1 scientific evidence for effectiveness (table 1). However, scale-up of potential interventions to mitigate HIV spread involves factors other than the hierarchy of scientific evidence. Criteria such as the cost of the intervention, the potential for side-effects, whether the intervention has other positive collateral benefits (as is the case for sexually transmitted infection treatment), and acceptability in the community need to be considered (discussed further by Bertozzi and colleagues[174]).

Irrespective of the level of evidence, male condoms are thought to be the gold standard for prevention of HIV as long as they are used consistently and correctly. The basis of this belief is laboratory data and observational studies (as opposed to randomised controlled trials with HIV infection as an outcome). In fact, the level of evidence needed for new methods surpasses what we accept for condoms. As with condoms, the full range of evidence (including biological plausibility, animal models, in-vitro models, observational studies, and the likelihood of increased effectiveness with increased adherence) should be considered before potentially effective interventions are discarded on the basis of the results of a few studies.

Current challenges for research

The disappointing results of many completed trials have revealed particular challenges to the investigation of biomedical HIV prevention.[175] Specifically, issues related to pregnancies that arise during the trial (forcing women to be withdrawn), unexpectedly low rates of new HIV infection, suboptimum product adherence, and the absence of a surrogate marker have been addressed. Another challenge concerns the standards of prevention services provided to trial participants.

Inextricable link between adherence and effectiveness

The importance of adherence in biomedical prevention has been extensively discussed.[175,176] Male condoms must be used consistently and correctly to prevent infection. Comparably, the prevention interventions that are being tested now need similar high levels of adherence to be effective. If adequate adherence is not achieved during a study, the true prevention effect will be masked.[66,79] The adherence achieved during a trial is probably higher than that which can be maintained under typical conditions after the study is completed. Adherence to long-term prevention regimens, especially when people are well, might be more difficult than adherence to treatment drugs when individuals are sick and need their medications to stay alive.

Research is needed on both how to improve and how to measure adherence. Different interventions require varying degrees of adherence to be able to measure effectiveness (table 1). Male circumcision (the only intervention with efficacy data from randomised controlled trials) needs only one decision: to obtain the intervention and no behaviour change. For other methods that depend on individual adherence, either daily decision or coitally dependent choices, the data from randomised controlled trials have been less clear.

No surrogates for HIV

The much publicised negative results of the cellulose sulphate and V520 vaccine trials have led some scientists to suggest that more basic science, preclinical, and early-phase research is needed before phase III trials are undertaken.[177–180] HIV infection is the definitive endpoint for both safety and effectiveness investigations, and there are no scientifically acceptable surrogates for it. The urgent need for additional methods of HIV prevention has accelerated research into phase III trials, partly because no intermediate outcome exists.[175] Indeed, trials of vaccines and some microbicide preparations have been initiated without scientific consensus that the product tested will have much effect. The rationale behind the decision to go ahead with these trials is that we simply do not know what does and does not work, and additionally we will learn valuable lessons from the trials, which we have. Ironically, surrogate endpoints can only be validated in a post-hoc manner from large safety and effectiveness studies powered for HIV infection as the endpoint.

Standard of prevention services in multicomponent interventions

To comply with ethical guidelines, we have reduced our ability to assess new prevention methods by comparing them to the best available prevention standards of care (eg, limitless sexually transmitted infection treatment; frequent, individualised, and expensive condom counselling). Such strategies are not representative of the standard of typical prevention services in the community and are not sustainable after completion of the trial. The complexity of the design is increased by addition of these packages to the intervention, so at best we can measure the marginal benefit of the new intervention compared with the effect of the ideal prevention package. Thus, the ability to detect any effect of interventions postulated to be moderately effective (eg, <50%) is reduced. Of equal concern, those individuals who live in the community outside the trial cannot benefit from high-intensity prevention services. This challenge will intensify should we include antiretroviral pre-exposure prophylaxis or circumcision in future trial prevention packages.

	Measurement method
UNGASS indicator 3: percentage of donated blood units screened for HIV in a quality-assured manner	FRAME Tool (Framework for Assessment, Monitoring and Evaluation of blood transfusion services): a rapid assessment method used by the WHO Global Database on Blood Safety
UNGASS indicator 5: percentage of HIV-positive pregnant women who receive antiretroviral drugs to reduce the risk of mother-to-child transmission	Programme monitoring methods, antenatal clinic surveillance or estimation modelling
UNGASS indicator 9: percentage of most-at-risk populations reached with HIV prevention programmes	Behavioural surveillance or other special surveys
UNGASS indicator 22: percentage of young people aged 15–24 years who are HIV infected	WHO guidelines for HIV sentinel surveillance
UNGASS indicator 23: percentage of most-at-risk populations who are HIV infected	UNAIDS/WHO Second Generation Surveillance Guidelines; Family Health International guidelines for sampling in population groups
UNGASS indicator 25: percentage of infants born to HIV-infected mothers who are infected	Statistical modelling based on programme coverage and efficacy studies

Table 4: **United Nations General Assembly Special Session (UNGASS) indicators for biomedical HIV prevention**

Way forward

A new lexicon for prevention

Although we have used a slightly new classification system for HIV prevention, some categories remain unchanged—eg, barrier methods, male circumcision, treatment of sexually transmitted infections to prevent HIV infection, and HIV vaccines. However, use of antiretroviral drugs to prevent HIV transmission has become a broad specialty of its own, encompassing many overlapping scientific issues.[181] As with hormonal contraception as a method to prevent pregnancy, future assessments of prevention with antiretroviral drugs should focus on methods of delivery (oral, topical [vaginal, rectal], injectable), dosing regimen (daily, monthly, intermittent or exposure related [before and afterwards]), single versus combination products, and what works in specific target populations (defined by risk, behaviour, and infection status). The present terminology, which groups methods for prevention of HIV transmission by mode of delivery (eg, microbicide preparations, pre-exposure prophylaxis), is outdated and inefficient. It has resulted in separate scientific meetings, publications, and discourse, and thus prevents a more integrated approach to prevention of HIV transmission.

Reduction of infectiousness

A focus lately has been on prevention programmes for individuals who have already tested positive for HIV and who may be at risk of transmitting the disease.[182] Initial approaches have emphasised behavioural interventions for infected individuals to reduce risky behaviour that could increase the likelihood of transmission (multiple concurrent partners, unprotected sex, unknown serostatus). The same focus is needed for biomedical interventions. Use of antiretroviral drugs and treatment of sexually transmitted infections (eg, HSV suppressive treatment for individuals co-infected with HSV and HIV) are being assessed in discordant couples as a way to reduce infectiousness. Data from clinical and observational studies are promising, and adherence might be greater among individuals who are already infected than among those who are only at risk.

Combination prevention packages

We will not find one solution for prevention.[183] Instead, partially effective interventions will be aggregated into combination prevention packages and targeted to specific individuals. This approach is especially important as we move from individual randomised trials to operational research for scale-up of large programmes.[184]

For example, to avoid risk compensation and to increase adherence, biomedical methods should be inextricably implemented together with behavioural interventions. Likewise, biomedical interventions, such as male circumcision, offer a unique opportunity for risk reduction counselling. Rather than trying to control for the effect of behaviour on biomedical methods, future studies should embrace this integration and use creative designs to examine strategies that offer a variety of prevention methods.[185] Inadequate adherence and sexual risk compensation might offset any positive effect at the population level of an intervention that has been proven to be effective in a trial. Careful monitoring of what happens in the community when the intervention is scaled up will be essential. All components of the intervention (biomedical and behavioural) should be clearly defined, replicable, and suitable for rigorous assessment.

Assessment of progress

The United Nations General Assembly Special Session (UNGASS) indicators are an attempt to measure universal markers of progress toward epidemic control through standardisation of methods, definitions, and periods to provide a universal framework to assess progress. Table 4 shows those indicators relevant to biomedical prevention (indicators for condom use are discussed by Coates and colleagues in this Series[186]). These indicators make the most of data routinely obtained through service provision and existing surveillance methods. Nevertheless, they can be challenging to measure on a continuous basis. Without substantial financial and technical support, few countries have the capacity to gather reliable and valid data about the indicators in a timely fashion.

Precise measures that characterise changes in prevalence or incidence require serological surveys of nationally representative samples or samples within subgroups. Such surveys have only recently been done in a small number of countries. However, they are very expensive and require a high degree of technical capacity; thus the recommendation is that the surveys be done only every 4–5 years. Additionally, such surveys are by definition done in populations that continue to face stigma and discrimination, including sex workers,

injection drug users, and men who have sex with men, further complicating the ability to gather valid data.

In the absence of empirical evidence, estimates of numbers of people in need (eg, coverage rates of prevention services required [indicator 9, table 4]) and estimates of numbers with incident infection (indicators 22, 23, 25) require epidemiological modelling, which although common, is nevertheless a move away from empirical data. For example, the percentage of young people aged 15–24 years who are infected with HIV (indicator 22) is calculated on the basis of data from pregnant women attending antenatal clinics in HIV sentinel surveillance sites throughout a country. This indicator provides a standard and inexpensive method of generating a proxy measure of changes in prevalence in the general population but it has to be extrapolated to men in this age-group and to women not seeking antenatal care.

The 2008 report of the global HIV/AIDS epidemic provides data from a substantial number of countries on the biomedical indicators.[187] However, worldwide data over time are available for only one indicator—the percentage of HIV-positive pregnant women who have received antiretroviral drugs to reduce the risk of mother-to-child transmission (34% in 2007 *vs* 14% in 2005).[187] Data for other indicators can provide the baseline for future comparisons.

On the basis of recommendations for male circumcision in 2007 from WHO and UNAIDS, indicators for monitoring progress of circumcision programmes are essential. Similarly, because contraception is an indispensable strategy to prevent mother-to-child transmission of HIV, another indicator that must be monitored is the percentage of HIV-infected women of reproductive age who do not want to become pregnant and who receive an effective contraceptive method. Finally, although not a population-level indicator of prevention, the number of new, safe, and effective biomedical interventions for prevention of HIV transmission that can be added to our arsenal should be monitored.

Conclusions

As is the case for all the papers in this Series, one of our main conclusions is that the compartmentalisation of prevention strategies into those that are biomedical, behavioural, and structural is artificial. Even a simple and successful biomedical strategy has the potential to alter individual behaviour and has to be scaled up in ways that affect structural institutions such as the health-care system. Hence, an integrated approach will inevitably be needed. New paradigms for HIV prevention, especially for biomedical interventions, must be considered because we do not have a simple and cheap method of HIV prevention.

As we approach the era of antiretroviral-based prevention (alone or as part of a combined package) to reduce HIV acquisition in uninfected individuals and to decrease HIV infectiousness in infected individuals, we should exercise restraint and not again set standards so high that moderate-level prevention strategies, which could offer measurable individual and population benefits, are destined not to demonstrate efficacy. We must assess new methods in light of the lessons learned from the past (challenges and suggested new directions) and be flexible about methodology and the interpretation of results. Even if successful, the operational issues of the sustained cost, the target population, methods of distribution, and long-term side-effects, remain paramount. Clearly this strategy will need both behavioural and structural components.

Conflict of interest statement

We declare that we have no conflict of interest.

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