Prevention of sexual transmission of HIV: real results, science progressing, societies remaining behind

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HIV spread has reached a turning point following decades of increasing and sustained incidence. An effective vaccine has not been developed, but critical breakthroughs with prevention based on antiretroviral treatment are promising. The new prevention technologies will have to be combined with condoms and incorporated into the mixes of combination prevention approaches that are tailored to the local epidemic and context. To address the implementation gap, more political will and leadership will be needed to overcome the socio-cultural, legal or religious barriers to prevention. We have learned that the generation of demand for HIV prevention is not easy, as for health promotion in general. Despite optimism about treatment as prevention, many western countries are facing an increase in new HIV cases, and HIV is no longer a collective concern. If we manage to find common ground on combination prevention, customize approaches to people's needs and exercise technical and political leadership, our decade may see the beginning of the end of the epidemic.

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Since the first reports on AIDS, knowledge on how to prevent new infections emerged rapidly, and sex was identified as the major mode of transmission in most countries [1,2]. Condoms were already available and factors affecting transmissibility such as sexually transmitted diseases, absence of male circumcision or advanced immunodeficiency were suggested in epidemiological studies [3,4]. Since there was no effective antiretroviral treatment available until 1996, HIV prevention was the only option in the AIDS response. This resulted in some initial successes in gay communities in high-income countries, thanks to major community mobilization, behavior change and condom use [5]. In the mid-1990s, for the first time, a decline in HIV prevalence and incidence was documented in heterosexual epidemics in developing countries – in the general population in Thailand and Uganda and the sex worker populations in Zaire and Kenya [6–9]. However, for several decades, options for HIV prevention were limited, with slow progress in the science of prevention or the development of much needed new tools and interventions – although major advances included the demonstration that mother-to-child transmission of HIV can be prevented, and that 'harm reduction' (needle exchange and substitution therapy) decreases the spread of HIV among injecting drug users [10,11].

Now, 30 years later, a wealth of scientific evidence has accumulated and insights into reducing HIV transmission have been gained [12–14]. Three intervention trials

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confirmed the protective effect of male circumcision, and antiretroviral therapy (ART)-based prevention with preexposure prophylaxis (PrEP) and early antiretroviral treatment showed efficacy in preventing HIV infections [15–18]. Prevention programming has evolved from mostly individual-level interventions toward combination prevention, including approaches that address social and structural factors and are better adapted to the local epidemiological, cultural and political contexts [14]. 'Know your epidemic' became the basis for more tailored prevention [19]. HIV incidence worldwide is declining; major progress in preventing HIV has been documented in populations, regions and countries [20,21]. It seems that, with the exception of the former Soviet republics, HIV spread has reached a turning point following decades of increasing and sustained incidence. However, new populations are being affected, such as MSM in Asia and Africa and injecting drug users in several sub-Saharan African countries.

Despite real progress, the HIV prevention field is struggling with numerous challenges: first, insufficient implementation in many populations. There is still no protective vaccine in sight; the debate continues about the most effective mix of combination prevention strategies for the most affected countries or populations. Leadership and management of prevention programs have generally been weak. As a result, in 2010 alone, another 2.6 million people acquired the virus, far more than the speed at which people with HIV can access treatment.

Technologies to reduce sexual transmission of HIV: from condoms to antiretroviral therapy and back?

The most effective way to control the HIV epidemic would be a highly protective HIV vaccine that is simple to administer and effective for all transmission modes. For decades, the hopes were high after the isolation of the virus that a vaccine was within reach. Thirty years later, it is likely that no vaccine will be available on the market despite major advances in our understanding of virology and immunology of HIV infection [22,23]. Although investments in vaccine research should continue, for now, the epidemic will have to be addressed with other approaches.

Male condoms have been available since day 1 of the epidemic and are recommended to prevent transmission during sex. In-vitro tests showed that condoms were impenetrable to particles of the size of HIV; and their effectiveness for the prevention of most sexually transmitted infections was well documented [24–26]. Although no randomized controlled trial was conducted for ethical reasons, the effectiveness of condoms to prevent HIV is estimated at 80–85% based on the data from longitudinal studies, and as high as 95% for consistent use [27,28]. Condom use is still one of the most effective ways to reduce the sexual transmission of HIV. The key determinant of condom effectiveness is adherence – as it is for most biomedical prevention tools, except male circumcision. The most convincing evidence of condom effectiveness at the population level comes from programs addressing HIV among sex workers and MSM and from national prevention successes such as in Thailand [20]. It is less clear how important condoms have been in curtailing the epidemic in the most affected countries in Africa, but this may reflect methodological challenges of attributing national declines of HIV infection. For example, an analysis of declining HIV trends in Zimbabwe showed that condoms did a play a role, as did a reduction in the number of casual partners and paying for sex [29]. Consistent condom use is generally less accepted among steady partners and in intimate relationships.

The need for prevention methods initiated and controlled by women was recognized early on [30]. The first female condom made of polyurethane is as effective as the male condom; similar efficacy was shown in one randomized controlled trial among women in Thailand [31]. However, high cost and low acceptability prevented this promising technology from being taken up widely, except for some pilot programs [32]. Newer versions of the female condom (made of nitrile or latex) are easier to use and expected to be more acceptable. The female condom is still the only highly effective female-initiated prevention method available on the market and, therefore, should be promoted as part of the prevention armamentarium.

The search for a vaginal cream or gel that women could use to protect themselves against HIV had already started in the late 1980s. Contraceptive products that are inexpensive, easily available over the counter and show in-vitro anti-HIV activity were tested first, but none showed protection and some even increased the risk of HIV acquisition [33–35]. The road toward an effective microbicide has been long and bumpy [36]. So far, only one trial testing a vaginal gel containing 1% tenofovir (TDF) showed a 39% protection when used 12 h before and 12 h after sex [18]. This breakthrough result was not confirmed in another study in which daily use of TDF vaginal gel was interrupted because of futility [37]. A confirmatory trial of a 1% TDF gel used before every sex act is now underway in South Africa [38]. The search for more effective topical antiretroviral drug-based prevention continues, focusing on potent antiretroviral products and combination products. Because adherence is key to effectiveness, the development of less coitally dependent delivery methods, such as vaginal rings with slow release, is a high priority, and much can be learned from the contraceptive field.

On the basis of the effectiveness of preventing mother-to-child transmission of HIV with antiretrovirals, low-dose oral TDF or a combination of emtricitabine and TDF (FTC/TDF) was tested for protection of HIV-negative people during sexual intercourse. Of six trials finalized among different populations, four showed protection ranging from 44 to 62% and two were interrupted because of futility (see Table 1) [38]. Despite major investments in adherence support in all those trials, the main explanation for suboptimal efficacy given by the investigators is low adherence. Subgroup analysis indicated higher efficacy of 73% (versus 44% overall) among MSM with high adherence to daily use of FTC/TDF [17]. Low antiretroviral concentration at the mucosal level may also play a role in explaining these discordant results [38,39].

The relationship between viral load suppression and reduction of HIV infectiousness is well established [40]. The meticulous HPTN052 trial showed that early ART leads to a 96% reduction in HIV transmission among HIV serodiscordant couples, establishing a proof of concept for ART as prevention [16]. This has opened up a new era for combination prevention in synergy with HIV treatment programs.

Whether those promising evolutions in ART-based prevention will also change the course of the epidemic will depend on several factors. For topical and oral PrEP, real-world user effectiveness, particularly in relationship to adherence, has to be clarified further. The feasibility of regular HIV testing and adherence support systems in different populations of PrEP users needs to be evaluated. Also, emergence of resistance to a class of drugs used for PrEP that is also first-line AIDS treatment remains a concern [41].

Investigating the effectiveness and feasibility of early ART as prevention at the population level is a high priority, with the Pop ART study (HPTN071) in Zambia and South African study being the most ambitious ones. The biggest unknown for the population-level effectiveness of treatment as prevention is the contribution of newly infected individuals, who are unlikely to be detected by early diagnosis and treatment, to the spread of HIV. The impact of increasing sexual risk behavior is unknown, and may outweigh the effect of reduction in transmissibility in the individuals. This was suggested by the increasing HIV incidence in the Netherlands in gay communities with a high access to ART [42]. This prevention strategy also raises the ethical question in the most affected countries of prioritizing those HIV patients who need ART for their immediate survival versus using ART for prevention. The deficit in access to treatment is illustrated by the fact that 6.6 million people in low-income and middle-income countries are now accessing treatment, representing 47% of those in need of treatment for their own survival [21].

While waiting for results from ongoing research, repositioning condom use at the center of HIV

Table 1. Biomedical tools to reduce probability of sexual transmission of HIV.

Tool	Efficacy/effectiveness	Adherence	Fe In	Other considerations
Male condom	From 80 to 95% (observational data); biological efficacy close to 100% as impenetrable barrier	For every coitus	N	Cheap; available over the counter; mixed acceptability; protects against most other sexually transmitted infections
Female condom	Similar to male condom (1 RCT)	For every coitus	Y	Medium cost; low acceptability
ART treatment	96% in serodiscordant couples (1 RCT and observational data evidence); population effectiveness unknown	Lifelong daily treatment for the infected person	NA	Implementation to test and treat whole populations, complex and costly; health systems to cope?; acceptability not yet known; ethical issues of prioritizing ART for patients with $CD4^+$ cell count <350 cells/μl; large treatment gap; effect of risk compensation?
Male circumcision	60% for female-to-male transmission (3 RCTs)	One decision for surgical procedure	N	Relevance mainly limited to eastern–southern Africa; implementation challenges; cultural and political barriers
PrEP				
Oral FTC/TDF	73% (49;85) in couples; 62% (34;78) in heterosexual men and women; 44% (15;63) in MSM; 0% (−69;41) in high-risk women	Daily	Y	Sustaining adherence challenging; regular HIV testing needed; emergence of drug resistance concern; cost: 'who will pay?'; side effects acceptable for use in HIV negative individuals?; acceptability may be higher than for condoms
Oral TDF	63% (22;83) in couples; 0% (–) futility in high-risk women; ongoing in IDU (RCT evidence)			
Vaginal TDF	39% (6;60) in high-risk women; 0% (–) futility in high-risk women; ongoing in high-risk women	Daily or for every coitus	Y	Adherence needs to be addressed; need for more potent class of drugs and new long-acting delivery methods

Fe In, female initiated; FTC, emtricitabine; NA, not applicable; PrEP, preexposure prophylaxis; TDF, tenofovir. Adapted and based on [27,28,31,32,37–39,41].

prevention is justified. New tools, if proven effective, should be combined with the old ones in the best possible way to obtain the highest coverage of sexual acts that have to be protected. Also, for eastern and southern Africa, that means greatly increasing the uptake of male circumcision.

Combination prevention: the evidence dilemma

Evidence-based HIV programming tends to favor technological approaches, as firm evidence for efficacy is easier to obtain [12,13]. However, all technologies also need behavioral strategies and mobilization of communities, in addition to services to deliver them. People are not passive recipients of technologies; they appropriate them with reference to their life and integrate them into their intimate relationships wherein gender and power dynamics are at play [43].

Addressing unsafe sexual behavior is an essential prevention component in its own right. Behavior change has been closely associated with prevention successes in various communities, but skepticism about their relevance remains, as the evidence base from randomized trials is poor [13]. We are confronted with a paradoxical situation of compelling evidence that HIV incidence is declining in many countries beyond natural history. This observation suggests that imperfect behavioral prevention approaches have an impact, whereas, on the contrary, trials evaluating behavioral approaches have showed no effect on HIV incidence [44]. The missing link may be an incomplete understanding of the extent to which sexual behavior change results from prevention programs in different contexts versus behavior change occurring, at least partly, because of external factors such as economic hardship. Identifying those social and contextual factors and addressing them, if possible, is an integral part of the concept of combination prevention.

There is now consensus in the HIV prevention community that combination prevention offers the best promise of success, but disagreement remains about the best mix of approaches and how to evaluate impact [20,45,46]. Components of combination prevention should be customized on the basis of the understanding of epidemic in a given context and guided by the best available plausible evidence of their effectiveness in these contexts. Finding the right balance between top–down essential prevention packages versus bottom–up community-owned context-specific processes is inherently a challenge, but both approaches are needed and should now meet each other.

It is time that the prevention world finds a common ground when it comes to promoting combination prevention, as policy paralysis may result in more infections and more deaths. Much more will have to be invested in rigorous learning while doing and partnerships between researchers, program implementers and affected communities are needed.

The implementation gap

Despite the increased understanding of which populations are at maximum risk for acquiring and transmitting HIV and the availability of effective prevention approaches, prevention coverage remains low in many key populations. Thus, worldwide in 2010, the median coverage of prevention services was 48% for sex workers, 55% for MSM and 32% for injecting drug users [47]. Those figures are likely to be overestimates because little systematic research has been done at the country level to obtain reliable estimates of the size of key populations and the coverage of interventions. The road from research to policy to implementation can be long, as illustrated by the fact that despite the evidence that male circumcision reduces female-to-male transmission by 60%, only 2.7% of the 20 million eligible men in 13 priority countries in southern Africa have been circumcised [48].

There is a wide spectrum of explanations for this implementation gap owing to socio-political, legal, cultural and religious barriers with regard to addressing marginalized groups such as sex workers or injecting drug users, addressing highly stigmatized or even criminalized same-sex sexual behavior or educating young people about sex [20].

The variable capacity of the public sector, nongovernmental organizations and communities to implement prevention activities, as well as the limited involvement of people with strong management expertise to coordinate and manage the programs at national level, contribute to the implementation gap. Short funding cycles affect long-term programming and sustainability. And finally, in the landscape of the 'multisectoral' response, the roles and responsibilities to coordinate the response and monitor progress have not always been clear.

The list of reasons for inaction is very long, but 30 years of AIDS response, with a consistent focus on a rights-based approach, has also illustrated that barriers can be overcome and the challenges addressed. Exceptional leaders have made a difference at international, national and local levels [49]. A recent example was Desmund Tutu from South Africa speaking out strongly in public against homophobia in Africa [50]. The evidence base for newly emerging HIV epidemics among hidden populations is growing, pointing to the prevention needs and calling for the creation of a more conducive environment [21,51]. Prevention programs at scale, like the Indian

initiative AVAHAN, are now being duplicated in Africa and the importance of management skills in program management is being recognized.

The most important lesson is that science can provide solutions tailored to the epidemic, but infections will only be prevented if political and technical leadership is sufficient to overcome the barriers and managerial capacity is adequate to make the programs work.

Generating demand for prevention

AIDS activism has been mostly directed toward treatment access, led by people living with HIV. A similar movement to demand prevention has not emerged spontaneously – although TAC in South Africa has been making considerable efforts [52]. It is understandable and a humanitarian imperative that attention goes first to those suffering and dying. The overwhelming and immediate impact of ART on saving lives was a strong mobilizing force and created an unprecedented movement of international solidarity and resource mobilization. Countries took pride in their ART scaling up efforts, the number of people initiated on treatment was publicized, and these reports became a tool for accountability rarely seen before in public health and international development.

Prevention efforts are less monitored and prevention successes less 'visible', primarily because of the difficulty of estimating events that did not occur. For an individual, the transmission happens mostly unnoticed and the infection can remain asymptomatic for several years. For societies, an outbreak of HIV can occur unnoticed for a long time until patients with AIDS present to health services. Moreover, there is still no biological test to easily measure HIV incidence. Moreover, defining prevention impact based on HIV prevalence trends is becoming increasingly complex owing to longer survival as a result of wider availability of antiretroviral therapy.

As in other fields of health promotion, HIV prevention is an uphill battle. In general, safer sex including condom use, refraining from penetrative sex or fidelity is perceived as less desirable. Leaders prefer to devote their energies to treatment instead of more controversial HIV prevention approaches, particularly in marginalized groups. The criminalization of homosexuality in 93 countries, even punished by the death penalty in seven countries, not only is one of the gross violations of human rights of our time but also makes HIV prevention very difficult [53].

In more liberal societies, the continuing high HIV rates among MSM have not generated sufficient community mobilization to turn the tide. The perception exists that HIV is not the threat as it once was; therefore there is less communication about HIV and social support, and community norms are shifting such that unsafe sex is more acceptable [54]. Despite optimism about treatment as prevention, several western countries have faced an increase in new HIV cases and unsafe sex among MSM in the last decade [55–58]. Paradoxically, antiretroviral therapy, which has saved millions of lives and prevented an unknown number of infections, may at the same time complicate HIV prevention.

We have learned over the years that demand generation for prevention is not easy, but the changing context and realities not only complicate prevention but also offer new opportunities. Critically important breakthroughs with ART-based prevention have given a boost to prevention research and brought prevention back to the center of the academic debates. And, the ongoing dialogue between the science and the affected communities could result in renewed, more effective, combination prevention strategies and frame HIV again as a collective concern [43].

The way forward: adopting a common ground and customized prevention

There is empirical evidence that HIV prevention is feasible and effective on a large scale. For the 2.6 million people newly infected with HIV in 2010, it was science not being applied rather than science failing to some extent.

Although academic debates on HIV prevention must continue and our knowledge base be sharpened, most attention should go to greatly implementing prevention programs for those at highest risk for HIV, as recommended by the AIDS 2031 consortium [59]. Such intensification of focused prevention and treatment programs must be accompanied by investments in better documentation of HIV transmission dynamics in key populations and continued evaluation of programs to adapt them when supported by new evidence. In light of the lessons learned from the past (no single magic bullet solution for prevention), the newly emerging biomedical tools will have to be incorporated carefully into new mixes of combination prevention approaches. Building new constituencies and looking for synergies with other health and development programs are a top priority for more efficient implementation.

If we collectively manage to develop common ground on combination prevention, customize programs to people's needs and exercise technical and political leadership, our decade may indeed see the beginning of the end of the HIV epidemic, but eliminating HIV with the current tools seems unlikely.

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Conflicts of interest

There are no conflicts of interest.

References

1. Jaffe H, Choi K, Thomas P, Haverkos HW, Auerbach DM, Guinan ME, *et al*. **National case–control study of Kaposi sarcoma and *Pneumocystis carinii* in homosexual men. Part 1: Epidemiologic results.** *Ann Intern Med* 1983; **99**:145–151.
2. Piot P, Quinn TC, Taelman H, *et al*. **Acquired immunodeficiency syndrome in a heterosexual population in Zaire.** *Lancet* 1984; **2**:65–69.
3. Cameron DW, Simonsen JN, D'Costa LJ, Ronald AR, Maitha GM, Gakinya MN, *et al*. **Female to male transmission of human immunodeficiency virus type 1: risk factors for seroconversion in men.** *Lancet* 1989; **2**:403–407.
4. Laga M, Taelman H, Van der Stuyft P, Bonneux L, Vercauteren G, Piot P. **Advanced immunodeficiency as a risk factor for heterosexual transmission of HIV.** *AIDS* 1989; **3**:361–366.
5. Winkelstein W Jr, Wiley JA, Padian NS, Samuel M, Shiboski S, Ascher MS, Levy JA. **The San Francisco Men's Health Study: continued decline in HIV seroconversion rates among homosexual/bisexual men.** *Am J Public Health* 1988; **78**:1472–1474.
6. Phoolcharoen W. **HIV/AIDS Prevention in Thailand: success and challenges.** *Science* 1998; **280**:1873–1874.
7. Stoneburner RL, Low-Beer D. **Population-level HIV declines and behavioral risk avoidance in Uganda.** *Science* 2004; **304**:714–718.
8. Ngugi EN, Plummer FA, Simonsen JN. **Prevention of transmission of human immunodeficiency virus in Africa: effectiveness of condom promotion and health education among prostitutes.** *Lancet* 1988; **2**:887–890.
9. Laga M, Alary M, Nzila N, Manoka AT, Tuliza M, Goeman J, *et al*. **Condom promotion, STD treatment leading to a declining incidence of HIV-1 infection in female Zairean sex workers.** *Lancet* 1994; **344**:246–248.
10. Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, *et al*. **Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group.** *N Engl J Med* 1994; **331**:1173–1180.
11. Wodak A, Maher L. **The effectiveness of harm reduction in preventing HIV among injecting drug users.** *NSW Public Health Bull* 2010; **21**:69–73.
12. Padian NS, Buve A, Balkus J, Serwadda D, Cates W Jr. **Biomedical interventions to prevent HIV infection: evidence, challenges, and way forward.** *Lancet* 2008; **372**:585–599.
13. Coates TJ, Richter L, Caceres C. **Behavioural strategies to reduce HIV transmission: how to make them work better.** *Lancet* 2008; **372**:669–684.
14. Gupta GR, Parkhurst JO, Ogden JA, Aggleton P, Mahal A. **Structural approaches to HIV prevention.** *Lancet* 2008; **372**:764–775.
15. Weiss HA, Halperin D, Bailey RC, Hayes RJ, Schmid G, Hankins CA. **Male circumcision for HIV prevention: from evidence to action?** *AIDS* 2008; **22**:567–574.
16. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, *et al*. **Prevention of HIV-1 infection with early antiretroviral therapy.** *N Engl J Med* 2011; **365**:493–505.
17. Grant RM, Lama JR, Anderson PL. **Preexposure chemoprophylaxis for HIV prevention in men who have sex with men.** *N Engl J Med* 2010; **363**:2587–2599.
18. Abdool Karim Q, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, *et al*. **Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women.** *Science* 2010; **329**:1168–1174.
19. UNAIDS. *Practical guidelines for intensifying prevention*. http://data.unaids.org/pub/Manual/2007/20070306_prevention_guidelines_towards_universal_access_en.pdf. (Accessed 6 March 2012)
20. Bertozzi SM, Laga M, Bautista-Arredondo S, Coutinho A. **Making HIV prevention programmes work.** *Lancet* 2008; **372**:831–844.
21. UNAIDS. *Epidemic report 2011*. http://www.unaids.org. (Accessed 6 March 2012)
22. Steinbrook R. **One step forward, two steps back-will there ever be an AIDS vaccine?** *N Engl J Med* 2007; **357**:2653–2655.
23. Day M. **AIDS expert doubts vaccine will be found in near future.** *BMJ* 2007; **334**:1133.
24. Van de Perre P, Jacobs D, Sprecher-Golberger S. **The latex condom, an efficient barrier against sexual transmission of AIDS related viruses.** *AIDS* 1987; **1**:49–52.
25. Lytle CD, Routson LB, Seaborn BG, Dixon LG, Bushar HF, Cyr WH, *et al*. **An in vitro evaluation of condoms as barriers to a small virus.** *Sex Transm Dis* 1997; **24**:161–164.
26. Holmes KK. **Effectiveness of condoms in preventing sexually transmitted infections.** *Bull World Health Org* 2004; **82**:454–461.
27. Weller S, Davis K. **Condom effectiveness in reducing heterosexual HIV transmission**. *Cochrane Database Syst Rev* 2002:CD003255.
28. Pinkerton SD, Abramson PR. **Effectiveness of condoms in preventing HIV transmission.** *Soc Sci Med* 1997; **44**:1303–1312.
29. Gregson S, Gonese E, Hallett TB, Taruberekera N, Hargrove JW, Lopman B, *et al*. **HIV decline in Zimbabwe due to reductions in risky sex? Evidence from a comprehensive epidemiological review.** *Int J Epidemiol* 2010; **39**:1311–1323.
30. Stein ZA. **HIV prevention: the need for methods women can use.** *Am J Public Health* 1990; **80**:460–462.
31. Fontanet AL, Saba J, Chandelying V. **Protection against sexually transmitted diseases by granting sex workers in Thailand the choice of using the male or female condom: results from a randomized controlled trial.** *AIDS* 1998; **12**:1851–1859.
32. UNFPA. **HIV prevention gains Momentum.** *Successes in female condom programming.* UNFPA, HIV/AIDS Technical Division; 2011.
33. Kreiss J, Ngugi E, Holmes K. **Efficacy of nonoxynol 9 contraceptive sponge use in preventing heterosexual acquisition of HIV in Nairobi prostitutes.** *JAMA* 1992; **268**:477–482.
34. Roddy RE, Zekeng L, Ryan KA. **A controlled trial of nonoxynol 9 film to reduce male-to-female transmission of sexually transmitted diseases.** *N Engl J Med* 1998; **339**:504–510.
35. Van Damme L, Ramjee G, Alary M, Vuylsteke B, Chandeying V, Rees H, *et al*. **Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: a randomised controlled trial.** *Lancet* 2002; **360**:971–977.
36. Jespers V, Laga M, Van Herrewege Y, Vanham G. **Microbicides a long and bumpy road to success?** *AIDS Rev* 2007; **9**:61–62.
37. National Institute of Allergy and Infectious Diseases (NIAID). *NIH modifies 'VOICE' HIV prevention study in women*. National Institutes of Health. http://www.nih.gov/news/health/sep2011/niaid-28.htm. [Accessed 28 September 2011]
38. Celum C, Baeten JM. **Tenofovir-based preexposure prophylaxis for HIV prevention: evolving evidence.** *Curr Opin Infect Dis* 2012; **25**:51–57.
39. Van der Straten A, Van Damme L, Haberer JE, Bangsberg DR. **How well does PREP work? Unraveling the divergent results of PREP trials for HIV prevention.** *AIDS* 2012; **26**. doi: 10.197/QAD.Ob013e3283522272.
40. Attia S, Egger M, Müller M, Zwahlen M, Low N. **Sexual transmission of HIV according to viral load and antiretroviral therapy: a systematic review and meta analysis.** *AIDS* 2009; **23**:1397–1404.
41. Detels R, Winslow DL, van Sighem A, Hollingsworth TD, Prins M. **Treatment as prevention: some additional thoughts.** *AIDS* 2012; **26**:519–520.
42. Bezemer D, de Wolf F, Boerlijst MC, *et al*. **A resurgent HIV-1 epidemic among men having sex with men in the era of potent antiretroviral therapy.** *AIDS* 2008; **22**:1071–1077.
43. Kippax S, Race K. **Sustaining safe practice: twenty years on.** *Soc Sci Med* 2003; **57**:1–12.
44. Halett TB, Gregson S, Mugurungi O, Gonese E, Garnett GP. **Assessing evidence for behavior change affecting the course of the HIV epidemic epidemics: a new mathematical modeling approach and application to data from Zimbabwe.** *Epidemics* 2009; **1**:108–117.

45. Laga M, Rugg D, Peersman G, Ainsworth M. **Evaluating HIV prevention effectiveness: the perfect as the enemy of the good.** *AIDS* 2012; **26**:779–783.
46. Padian NS, McCoy SI, Balkus JE, Wasserheit JN. **Weighing the gold in the gold standard: challenges in HIV prevention research.** *AIDS* 2010; **24**:621–635.
47. *UNAIDS country progress report 2010*. www.unaids.org.
48. Dickson KE, Tran NT, Samuelson JL, Njeuhmeli E, Cherutich P, Dick B, *et al*. **Voluntary medical male circumcision: a framework analysis of policy and program implementation in eastern and southern Africa.** *PLoS Med* 2011; **8**: e1001133.
49. Piot P, Russell S, Larson H. **Good politics, bad politics: the experience of AIDS.** *Am J Public Health* 2007; **97**:1934–1936.
50. Duby Z. **Realities and cultural challenges in Africa.** *Oral presentation at the ICASA Conference*; 4–8 December 2011; Addis Abeba, Ethiopia.
51. Mumtaz G, Hilmi N, McFarland W. **Are HIV epidemics among men who have sex with men emerging in the Middle East and North Africa? A systematic review and data synthesis.** *PLoS Med* 2010; **8**:e1000444.
52. Piot P, Bartos M, Larson H, Zewdie D, Mane P. **Coming to terms with complexity: a call to action for HIV prevention.** *Lancet* 2008; **372**:845–859.
53. Human rights Watch. *Report of the United Nations High Commissioner for Human Rights. Discriminatory laws and practices and acts of violence against individuals based on their sexual orientation and gender identity*. http://www.un.org/apps/news/story.asp?NewsID=40743. (Accessed 6 March 2012)
54. Morin SF, Vernon K, Harcourt J, Steward WT, Volk J, Riess TH, *et al*. **Why HIV Infections have increased among men who have sex with men and what to do about it: findings from California Focus Groups.** *AIDS Behav* 2003; **7**:353–362.
55. Sullivan PS, Hamouda O, Delpech V. **Reemergence of the HIV epidemic among men who have sex with men in North America, Western Europe, and Australia.** *Ann Epidemiol* 2009; **19**:423–431.
56. Heuker J, Sonder GJ, Stolte I, Geskus R, van den Hoek A. **High HIV incidence among MSM prescribed postexposure prophylaxis, 2000–2009: indications for ongoing sexual risk behaviour.** *AIDS* 2012; **26**:505–512.
57. Le Vu S, Le Strat Y, Barin F, Pillonel J, Cazein F, Bousquet V, *et al*. **Population-based HIV-1 incidence in France, 2003-08: a modelling analysis.** *Lancet* 2010; **10**:682–687.
58. McDaid LM, Hart GJ. **Sexual risk behaviour for transmission of HIV in men who have sex with men: recent findings and potential interventions.** *Curr Opin HIV AIDS* 2010; **5**:311–315.
59. The AIDS 2031 consortium. *AIDS Taking a long-term view*. www.aids2031.org.