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## HIV-prevention science at a crossroads: advances in reducing sexual risk

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### Abstract

**Purpose of review**—We review the current state of evidence-based prevention strategies for reducing sexual transmission of HIV. The combined programmatic and scientific efforts through 2008 to reduce sexual transmission of HIV have failed to reduce substantially the global pandemic.

**Recent findings**—Prevention interventions to reduce HIV infection target behavioral, biomedical, and structural risk factors. Some of these prevention strategies have been evaluated in randomized clinical trials (RCTs) with HIV seroincidence endpoints. When RCTs are not feasible, a variety of observational and quasiexperimental research approaches can provide insight as to program effectiveness of specific strategies. Only five RCTs have demonstrated a notable decrease in sexually acquired HIV incidence. These include the Mwanza study of syndromic management of sexually transmitted diseases and three male circumcision trials in East Africa; a microbicide trial reported in 2009 shows substantial promise for the efficacy of PRO 2000 (0.5% gel).

**Summary**—The combined programmatic and scientific efforts to reduce sexual transmission of HIV have made incremental progress. New prevention tools are needed to stem the continued spread of HIV, though microbicides and vaccines will take many more years to develop, test, and deploy. Combination strategies of existing modalities should be tested to evaluate the potential for more proximate prevention benefits.

### Keywords

circumcision; HIV; microbicide; microbicide; prevention; sexual behavior; sexually transmitted disease

### Introduction

The spread of the human immunodeficiency virus (HIV) represents the worst global pandemic since the bubonic plague in 14th century Europe and Asia. Between 1981 and 2007, 64.9 million people are estimated to have been infected with HIV of whom about half have died [1]. In 2007 alone, 2.5 million persons were infected with HIV –90% of whom

live in Sub-Saharan Africa, Asia, and Eastern Europe [2]. About 80% of all newly infected persons acquired infection through sexual contact [3,4]. The combined programmatic and scientific efforts to reduce sexual transmission of HIV have failed to address the pandemic effectively.

Diversity in how the epidemic manifests itself is a key challenge. The virus has considerable genetic variability, inhibiting the development of an effective HIV vaccine. The diversity of infected populations reflects the diverse modes of transmission – heterosexual, homosexual, needle-related, blood and blood product-related, and perinatal. Diversity in the route of transmission and in the burden of disease presents a mosaic of dynamic subepidemics, each driven by a variety of behavioral, structural and biological risk factors. In this review, we emphasize evidence-based prevention efforts targeting sexual transmission, particularly those published in 2007 and 2008.

## HIV prevention: a failure of implementation

A failure of vision and/or political commitment to implement what we know works has limited the success of HIV-prevention efforts. UNAIDS estimated that in 2005, fewer than one in five people could access any known HIV-prevention strategies [5]. When prevention interventions are accessible and coupled with behavioral changes substantial decreased in HIV incidence can occur. The ‘ABC’ of delaying sexual debut in youth (abstinence), reducing the number of sexual partners and reducing concurrent sexual relationships (be faithful), and correct, consistent condom use reduced HIV seroincidence in Uganda, Thailand, and perhaps elsewhere [6–10]. As background HIV prevalence rises within populations, there is a poor correlation between personal risk factors and probability of HIV acquisition. The probability of exposure per sexual encounter, related to background prevalence, becomes the single biggest risk factor for getting infected in generalized epidemics and within at-risk subgroups.

This epidemic has been further exacerbated by ignoring the complex array of societal and contextual factors that increase a person’s risk for HIV infection. Focusing exclusively on individual and personal risk factors and dependence on intrinsically driven behaviors will not adequately address current epidemic trajectories. Community stigma inhibits community education, testing for HIV, and access to prevention and care. Sex and power dynamics including survival strategies and economic pressures are critical extrinsic factors that diminish individual autonomy and control of HIV-risk reduction. To reduce sexual risk inherently requires, at a minimum, engaging the sexual dyad, whether heterosexual or homosexual. Exclusion of women from the formal economy, as well as societal expectations of subservience and procreation fuel vulnerability of women through the adoption of a variety of survival strategies. This vulnerability can manifest in sex work to feed one’s children, sexual liaisons to enable school continuation, remaining in abusive marital relations, sexual exploitation in the work-place, forced marriage, and exposure to life-threatening HIV/AIDS stigma [11–14]. These are best described in Africa and Asia, but may apply anywhere in the world.

## Preventing HIV infection: randomized controlled trials

Observational studies have generated a substantial body of literature on a range of biomedical, behavioral, and structural interventions associated with lowered HIV-risk behaviors and/or HIV incidence [15–17]. However, prevention interventions have only rarely proved efficacious when tested in randomized clinical trials (RCTs) with HIV endpoints. Furthermore, there has been a poor correlation between behavior change and reduction in HIV-incidence rates. Between 2005 and 2007, several important, innovative Phase III HIV prevention RCTs were in progress (Table 1) [18–39].

By 2007, as the trials reached completion or were stopped early for reasons of harm or futility, negative sentiments about HIV prevention science started to emerge. This situation was most notable in the vaccine and microbicide fields. Just months after a 2008 *Science* [40] article that discussed some of the current failures in the microbicide field and questioned the future of the microbicides, a promising microbicide result for PRO 2000 (0.5%) gel (discussed later) was presented at the 16th Conference on Retroviruses and Opportunistic Infections [41\*]. This good news notwithstanding, most recent prevention trials (with the important exception of the male circumcision trials) have not demonstrated efficacy in preventing HIV infection [27\*\*,29,30,33,42].

The number of recently completed but unsuccessful prevention trials mask important progress in the efforts to reduce HIV infection. Building on observations in couples from Quinn *et al.* [43] and Fideli *et al.* [44] on the close correlation between viral load and HIV transmission, new opportunities for HIV prevention have emerged through expanding access to testing and knowledge of HIV status, linked to antiretroviral therapy (ART) for infected persons. This ‘test and treat’ concept has potential as an intervention for decreasing viral load in communities and thus reducing the probability of transmission at a population level. The use of ART as a prevention tool has already proven effective in prevention of mother-to-child HIV transmission (PMTCT) – women who are given ART during pregnancy and postpartum have a significantly decreased risk for transmission of virus to their newborn [45–47]. However, use of ART, as a prevention tool requires patients to know their HIV-positive status, have access to care, and to adhere to medications necessary to lower viral loads and minimize antiviral drug resistance. With six drug classes now in use (<http://www.fda.gov/oashi/aids/virals.html>, accessed 30 March 2009), several of which are in affordable generic formulations, advances in the field of antiviral chemotherapy have made effective viral load reduction even more feasible.

### Vaccines

The ‘Step’ study of the MRK Ad5 gag/pol/nef HIV-1 vaccine did not indicate vaccine benefit in adenovirus-seronegative persons and showed higher HIV seroconversion in adenovirus-seropositive persons [37\*\*]. Deep tissue HIV invasion may occur in just 2 weeks or less, demonstrating how hard it will be to use a human immunologic barrier to block HIV, given the current state of knowledge [48].

### Physical barriers

Although the effectiveness of male condoms is exceedingly well documented despite the lack of a RCT [49], condom usage rates are still low in most high-risk persons globally. The Zimbabwean MIRA trial did not suggest the female diaphragm to be more successful in preventing HIV compared with condom use alone [31]. Efficacy of female condoms remains unknown and unstudied in clinical trials; effectiveness data are also sparse.

### Chemical barriers (topical microbicides)

Cellulose sulfate gel, 1.0% C31G (SAVVY), Carraguard, and Buffer-gel products failed to prevent HIV transmission in prevention RCTs [32–36,41\*,50]. However, PRO 2000 (0.5%) gel, a nonspecific entry/fusion inhibitor, was 30% effective ( $0.05 < P \leq 0.10$  against placebo gel or no gel groups,  $P < 0.05$  against placebo and no gel groups combined) in reducing HIV incidence [41\*]. Microbicide trials with antiretroviral active agents (e.g., tenofovir) are in progress [51].

### Oral prophylactic antiretroviral therapy

Animal data suggest that ART can be given before HIV exposure and continued for several weeks after exposure to reduce risk of HIV transmission [52–55]. Preexposure prophylaxis (PrEP), some with postexposure (PEP) components are in progress worldwide in both men who have sex with men (MSM) and at-risk heterosexuals. Perhaps the most promising product (as of this 2009 writing) is tenofovir combined with emtricitabine (TDF/FTC or Truvada) due to its lower likelihood of emerging drug resistance, high genital tract concentrations, and long half-life [56,57]. If effective, implementation will be challenging, especially in more resource-limited settings where even HIV-infected persons are underserved with antiretroviral services. Nonetheless, if drug prices fall, decision analysis models suggest it could be a cost-effective intervention [58].

### Male circumcision

Randomized clinical trials in South Africa, Uganda, and Kenya demonstrated approximately 50% seroincidence decline in circumcised heterosexual men [23–25]. This has galvanized an effort to expand such services in high prevalence venues, given their high cost efficiency [59–61]. As scale-up occurs, mitigation of harm from suboptimal surgery will be a challenge [62–64]. Benefits of circumcision to MSM are unknown, and would only be expected to benefit men who are exclusively (or almost exclusively) insertive in their sexual acts [65,66].

### Control of sexually transmitted infections

The suppression of herpes simplex virus type-2 infection with chronic acyclovir did not reduce HIV seroconversions in either MSM in the Americas or with high-risk heterosexual women in Africa [21\*\*,22\*]. This was disappointing given the very strong correlation of HSV-2 infection with risk of HIV acquisition reported in observational studies; many in the field expected HSV-2 suppression to mimic adult male circumcision successes [67]. In addition to these more recent trials, previous community-RCTs have examined the effect of improved STI treatment on HIV transmission [18–20,26]. The results of these studies were mixed suggesting that treatment of bacterial STI may be more effective in preventing HIV infection in settings with low-to-emerging HIV epidemics or mature epidemics with high incidence and where there is a high background prevalence of bacterial STI [68–71].

### Behavior change and youth

Work is in progress on an array of approaches and strategies [15]. A meta-analysis suggested no efficacy of abstinence-only-based behavior change in preventing HIV, but promise was shown for more comprehensive ‘abstinence-plus’ programs [72–74]. A community RCT in Tanzania did not demonstrate reduced HIV incidence in adolescent girls, despite improving knowledge, attitudes, and reducing some sexual risk behaviors in boys [42]. The Stepping Stones initiative in rural South Africa was a behavioral intervention that did not reduce incidence of HIV in 15–26 year olds, but had a significant impact on reducing HSV-2 incidence and intimate partner violence [27\*\*]. However, this study did not demonstrate a change in HIV rates, reinforcing that there are no good surrogate markers for HIV incidence itself [27\*\*]. A RCT of risk reduction among Zimbabwean adolescents is in progress, having recruited a very high proportion of youth into the intervention vs. control groups before they became sexually active [29].

### Structural intervention

Structural interventions are policy changes that encourage risk reduction. Raising cigarette taxes to discourage youth from smoking and banning smoking in public indoors areas are two familiar examples. The Microfinance for AIDS and Gender Equity (IMAGE) study

combined a microfinance program with training in sex–power relationships and HIV-risk reduction in rural South Africa. Reductions in levels of intimate-partner violence were significant in the intervention arm along with reductions in HIV-risk behaviors [75], but HIV rates did not differ [30]. Although HIV results were disappointing, the RCT illustrates how multi-component interventions will be used to try to break the cycle of HIV transmission.

In summary, 28 years into the pandemic only five randomized controlled trials have demonstrated a decrease in HIV-incidence rates. The Mwanza trial demonstrated a 42% reduction in HIV seroincidence in persons living in communities with immediate availability of syndromic management of bacterial sexually transmitted diseases (STDs) [20]. This promising finding was not observed in the context of three subsequent phase III RCTs of STD intervention studies in the Rakai, Masaka, Manicaland regions [18,19,26]. A microbicide has shown promise in the HPTN035 study of PRO 2000 0.5% gel [41\*]. The protective effect of medical male circumcision in preventing female–male transmission of HIV has been confirmed consistently in three independently conducted phase III RCTs [23–25]. The translation of these impressive findings has been limited by political, cultural/social and programmatic challenges [59,61,62,76–81]. This leaves us with a limited arsenal of proven HIV-prevention strategies, though circumstantial evidence of male condom efficacy and salutary benefits of delayed sexual debut and partner reduction remain compelling.

## Methodological challenges

Notwithstanding the scientific challenges in preventing HIV infection, the conduct of RCTs in HIV prevention has numerous additional challenges in design, selecting appropriate outcome measures for both efficacy and effectiveness studies including the lack of proxy markers for protection [82\*,83]. A key factor contributing to small effect size of interventions is the ethical obligation to provide risk reduction education in comparison or control populations, even in settings where there remains limited access to prevention in the real world. For example in the MIRA RCT, female diaphragms and condoms were compared against condoms alone [31]. Although women using diaphragms had the same transmission rates as those whose partners used condoms, it was interpreted widely that diaphragms were ineffective. A more correct interpretation was that they might have been equally efficacious as condoms, as condom use in the diaphragm group was uncommon, despite encouragements for their use.

The prevention community has also been slow to embrace combination prevention efficacy trials despite what we have learned from therapeutic trials or strategies in the PMTCT field about the importance of using more comprehensive intervention strategies targeting all potential routes of viral entry and/or replication. Instead, HIV-prevention efforts have adopted the approach of incremental/attributable risk reduction. Although these unitary strategies for HIV prevention are alluring in theory (lower cost, ease of implementation); research investments (from the USA National Institute of Allergy and Infectious Diseases, the United Kingdom Medical Research Council, and the Bill and Melinda Gates Foundation, for example) have disproportionately emphasized ‘magic bullets’ for HIV prevention (i.e., prophylactic vaccines, PrEP, and microbicides) compared with more complex multicomponent interventions. The latter could have epidemic impact of more immediacy and effectiveness [37\*\*,40,84]. The authors of this review believe that future trials must combine interventions, each with small effects but with the potential for synergy if combined. Prevention science strategies and trial conduct needs to take into account the myriad of biological, behavioral, and structural factors that increase a person’s risk for infection at multiple levels. Rarely does an individual at risk of getting infected with HIV have a single intrinsic factor that might lead to infection.

## Conclusion

A diverse biomedical and biobehavioral portfolio of research is essential for us to make progress in HIV control. Building on the tools provided by basic, clinical, and social sciences, we need to move new products and strategies into rigorous field testing. Implementation of single modality interventions will not solve the problem. History has taught us through PEPFAR and the Global Fund to Fight AIDS, tuberculosis and malaria that 'where there is a will there is a way'. These therapeutic implementation successes have also highlighted the numerous challenges in the context of failing healthcare delivery systems, inadequate infrastructure and limited human resources to attain access, coverage and acceptability levels needed to make a difference to current epidemic trajectories [85,86,87\*].

Vaccines and microbicides are still seen as the holy grails of prevention as reflected in budgetary allocations. Although these approaches will remain an important part of our medium-to long-term strategy, we must invest in strategies with impact in the shorter term. Combinations of interventions based on existing tools such as the delaying sexual debut, partner fidelity, use of condom barriers (the abstinence, be faithful, correct condom use 'ABC' mantra), and male circumcision will be needed to complement whatever biomedical interventions are made available and are used by the target communities. We believe that the lessons learned suggest that multicomponent, multilevel interventions with careful monitoring and evaluation in implementation will be more likely to succeed than unitary biomedical approaches.

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## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 337–338).

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- 87•. Granich RM, Gilks CF, Dye C, et al. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet* 2009;373:48–57. This fanciful model examined the effectiveness of both increased HIV testing and early initiation of ART. Although the model assumptions are unrealistic, it is a stimulating examination of the potential for ‘test and treat’ initiatives as a HIV prevention strategy. [PubMed: 19038438]

Table 1

Summary of recent clinical trials of HIV prevention

Author	Intervention	Population	Outcome	Strength of association (95% CI)	Comments
<b>Selected prevention trials in progress with HIV endpoints</b>					
HPTN 043 Protocol chair: T.J. Coates	Expanded VCT and bridging to care	South Africa; Tanzania; Zimbabwe; Thailand	Seroprevalence surveys (to estimate HIV incidence)	In progress	Project Accept, community-RCT in progress to test impact of expanded HIV testing and community mobilization on HIV incidence
HPTN 052 Protocol chair: S. Cohen	Reduce partner transmission via early ART	Malawi; South Africa; Zimbabwe; India; Thailand; Botswana	Seroconversion in discordant couples	In progress	Individual randomization of discordant couples to assess whether or not early treatment of the HIV+ person reduces HIV infections in partner
<b>Control of STDs to reduce HIV acquisition</b>					
Waver <i>et al.</i> [18]	Periodic mass therapy for STI	Rakai, Uganda	HIV incidence	RR = 0.97 (0.81–1.16)	Mature HIV epidemic, relatively low rates of curable STIs, high HSV-2 rates, mass periodic STD therapy
Kamali <i>et al.</i> [19]	STD syndromic management	Masaka, Uganda	HIV incidence	RR = 0.91 (0.56–1.47)	Mature HIV epidemic, relatively low rates of curable STIs, most infections occurred between regular partners
Grosskurth <i>et al.</i> [20]	STD syndromic management	Mwanza, Tanzania	HIV incidence	RR = 0.58 (0.42–0.79)	Syndromic management worked to reduce HIV incidence. High curable STI rates among core transmitters.
Celum <i>et al.</i> [21**]	HSV-2 suppression	South Africa; Zimbabwe; Zambia; Peru; USA	HIV incidence	RR = 1.16 (0.83–1.62)	The larger of the two HSV-2 suppression studies, it suggests that nose of acyclovir given to participants may not have been sufficient to reduce HIV susceptibility resulting from HSV-2 infection.
Watson-Jones <i>et al.</i> [22*]	Herpes simplex virus type 2 (HSV-2) suppression	Tanzania	HIV incidence	RR = 1.08 (0.64–1.83)	HSV-2 suppression trial showed no benefit for HIV prevention.
<b>Adult male circumcision</b>					
Auvert <i>et al.</i> [23]	Adult male circumcision	Orange Farm, South Africa	HIV incidence	RR = 0.49 (0.28–0.84)	All three trials with remarkably similar results, the strongest effect size of any RCTs for prevention with HIV end points. Male circumcision seen as a powerful tool to reduce HIV transmission; its utility in public health practice now being assessed.
Gray <i>et al.</i> [24]	Adult male circumcision	Rakai, Uganda	HIV incidence	RR = 0.47 (0.28–0.78)	
Bailey <i>et al.</i> [25]	Adult male circumcision	Kisumu, Kenya	HIV incidence	RR = 0.40 (0.24–0.68)	

Author	Intervention	Population	Outcome	Strength of association (95% CI)	Comments
<b>Behavior change-based interventions</b>					
Gregson <i>et al.</i> [26]	Integrated community and clinical HIV control*	Manicaland, Zimbabwe	HIV incidence	RR = 1.27 (0.92–1.75)	No notable impact on HIV seroincidence.
Jewkes <i>et al.</i> [27]**	Stepping Stones behavioral intervention	South Africa	HIV incidence	RR = 0.95 (0.67–1.35)	A significant decrease in HSV-2 acquisition was observed as well as a decrease in intimate partner violence suggesting that study impacted HIV-risk behaviors but not HIV transmission.
Latkin <i>et al.</i> [28]	Network-oriented peer education	Thailand; USA	Behavioral endpoints†	No significant decrease in risk behaviors (sexual or injection)	Incidence rates were not as high as expected in either arm of the study. It was underpowered to determine the effect of peer education on HIV incidence.
Cowan <i>et al.</i> [29]	Multicomponent behavioral intervention in adolescents	Zimbabwe	HIV incidence	In progress	Baseline data suggest that the intervention was implemented prior to onset of sexual activity of adolescents.
Pronyk <i>et al.</i> [30]	Microfinance-based structural Intervention	South Africa	HIV incidence, unprotected sex, intimate partner violence	RR = 1.06 (0.66–1.69), RR = 0.89 (0.66–1.19), RR = 1.02 (0.85–1.23)	The study lacked the precision necessary to adequately measure effect size. The number of villages included in the study was determined by feasibility of implementing the intervention, and was not necessarily large enough to detect a small effect size.
Padian <i>et al.</i> [31]	Diaphragm	South Africa, Zimbabwe	HIV incidence	RR = 1.05 (0.84–1.32)	Condoms were used extensively in the control arm and not in the intervention arm. This suggests that diaphragm was as efficacious as condoms at preventing HIV acquisition given that risk for acquisition was approximately equal.
<b>Microbicide trials</b>					
Halpern <i>et al.</i> [32]	Microbicide (Cellulose sulfate gel)	Nigeria	HIV Incidence	HR = 0.8 (0.3–1.8)	This trial was suspended early due to data from a parallel trial, which suggested that cellulose sulfate increased risk for HIV acquisition.
Abdool Karim <i>et al.</i> [41*]	Microbicide (0.5% PRO 2000 gel)	Malawi, South Africa; Zambia; Zimbabwe; United States	HIV incidence	HR = 0.7 (0.4–1.0)	30% efficacy suggested borderline statistical significance.
Feldblum <i>et al.</i> [33]	Microbicide (0.1% SAVVY gel)	Nigeria	HIV incidence	HR = 1.7 (0.9–3.5)	Trial was halted due to lower-than-expected HIV incidence among participants. There was not adequate power to detect effect of SAVVY gel.
Peterson <i>et al.</i> [34]	Microbicide (0.1% SAVVY gel)	Ghana	HIV incidence	HR = 0.88 (0.33–2.27)	Trial was halted due to lower-than-expected HIV incidence among

Author	Intervention	Population	Outcome	Strength of association (95% CI)	Comments
Skoler-Karppoff <i>et al.</i> [35]	Microbicide (Carraguard)	South Africa	HIV incidence	HR = 0.87 (0.69–1.09)	participants. There was not adequate power to detect effect of SAVVY gel. Low levels of reported adherence prevented the trial from having the power needed to detect efficacy of Carraguard.
Van Damme <i>et al.</i> [36]	Microbicide (6% cellulose sulfate gel)	Benin; South Africa; India; Uganda	HIV incidence	HR = 1.61 (0.86–3.01)	Safety concerns for this product.
<b>Vaccine trials</b>					
Buchbinder <i>et al.</i> [37*]	Cell-mediated immunity vaccine	North America; South America; Caribbean; Australia	HIV incidence	HR = 1.2 (0.6–2.2)	This trial was halted early because protective efficacy was not observed in males in this cohort. Efficacy assessment could not be determined in women because of low HIV acquisition rates.
Flynn <i>et al.</i> [38]	Recombinant glycoprotein vaccine (VaxGen; bivalent subtype B/B rgp120)	North America	HIV incidence	Vaccine efficacy: 0.06 (317–24)	No vaccine benefits or harms noted.
Pitisuttithum <i>et al.</i> [39]	Recombinant glycoprotein vaccine (VaxGen; bivalent subtype B/E rgp120)	Thailand	HIV incidence	Vaccine efficacy: 0.1 (330.8–23.8)	No vaccine benefits or harms noted.

\* This included: peer education, condom distribution, and syndromic management for sexually transmitted infections.

† The study was terminated early due to insufficient incidence in study sites. Behavioral data were collected for secondary outcome measures and was used in final analysis. VCT, voluntary counseling and testing.