

# Behavioral and Biomedical Combination Strategies for HIV Prevention

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Around 2.5 million people become infected with HIV each year. This extraordinary toll on human life and public health worldwide will only be reversed with effective prevention. What's more, in the next few years, it is likely at least, that no single prevention strategy will be sufficient to contain the spread of the disease. There is a need for combination prevention as there is for combination treatment, including biomedical, behavioral, and structural interventions. Expanded HIV prevention must be grounded in a systematic analysis of the epidemic's dynamics in local contexts. Although 85% of HIV is transmitted sexually, effective combinations of prevention have been shown for people who inject drugs. Combination prevention should be based on scientifically derived evidence, with input and engagement from local communities that fosters the successful integration of care and treatment.

History has taught us that the way to eradicate a global viral epidemic is to design, mass produce, and then systematically vaccinate the population at risk with an effective prophylactic vaccine (Fifty-Fifth World Assembly 2008; <http://www.who.int/mediacentre/news/releases/releasewha01/en/index.html>). Past experience has also shown that the path to an effective AIDS vaccine may be long and complicated (Nabel 2001; Barouche 2008). Although the modest RV144 or “Thai” vaccine trial efficacy results in 2009 provided the first hope that a prophylactic HIV vaccine may be possible (Rerks-Ngarm et al. 2009), with almost 60

million men, women, and children having been infected and more than 25 million attributable deaths, 30 years of this epidemic has taken a monstrous toll. More worrying still, modeling exercises have indicated that staggering numbers of new infections may occur given current infection rates. The world may be facing 20–60 million new HIV infections in the 15–20 years it may take to develop and evaluate a highly efficacious prophylactic vaccine. Such alarming projections emphasize the urgency of finding effective alternative approaches to prevention more immediately (Legakos and Gable 2008).

L.-G. Bekker et al.

King Holmes has proposed a synergistic combination of sociobehavioral and medical interventions and coined the phrase highly active retroviral prevention (HARP). He further stated “only fools today still advocate a single method of HIV prevention” (Vandenbruaene 2007). Coates and colleagues captured this concept previously (Fig. 1) (Coates et al. 2008).

The emphasis in prevention research in 2011 has therefore shifted to the design and evaluation of combination prevention packages. The justification for this is summarized in Table 1.

A challenge for researchers in the HIV prevention field is to design combination packages that are feasible, effective, affordable, community- and population-specific, and acceptable. This article examines the available biomedical and behavioral interventions and the evidence of their suitability for inclusion in combination prevention packages.

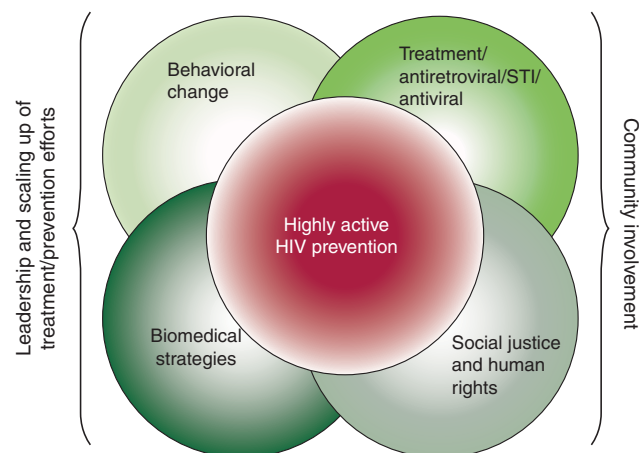
### KNOW YOUR EPIDEMIC, KNOW YOUR RESPONSE

It is likely that prevention packages will not be a “one size fits all endeavor” and ideal menus will need to be tailored for specific behaviors, regions, and risk categories. This requires that physicians and public health workers know their local populations and the basis for transmission and thus tailor responses accordingly.

The rapidly changing face of the epidemic calls not only for increased epidemiologic HIV transmission and behavioral surveillance but also for nuanced investigation that accounts for preference, social, cultural, and gender contexts. To this end, UNAIDS has launched a program entitled “know your epidemic, know your response” which encourages country-led investigation of the relevant drivers and risk behaviors (UNAIDS 2007; Wilson and Halperin 2008).

### Which Level of Evidence?

Padian and colleagues (2010) have examined all randomized controlled trials with HIV transmission as an endpoint performed in the last 2 decades (summarized and updated in Table 2) and asked what types of evidence will be considered in the selection of interventions in prevention packages of the future. Public health agencies have long recognized the shortfalls posed by relying solely on randomized controlled trial (RCT) data and have consequently developed guidance that also considers a variety of other data sources (Padian et al. 2010). HIV prevention researchers may need to adopt similar strategies. Furthermore, a clear understanding of how partially efficacious interventions may be combined for synergistic or additive effect remains a challenge (Piot et al. 2008).



**Figure 1.** Highly active HIV prevention, a term coined by King Holmes, University of Washington School of Medicine, Seattle, WA. (STI) Sexually transmitted infections (Coates and Gable 2008).

**Table 1.** Reasons for a shift to prevention packages

Concept	Reason	Reference
1.	It is clear from results of recent trials that there will be no single “magic bullet” for HIV prevention in the near term.	Padian et al. 2010
2.	Interventions with modest levels of effect might lead to more substantial efficacy overall if combined.	Auerbach and Coates 2000
3.	Current biomedical interventions are affected by human behavioral factors (adherence, risk compensation) and will rely on sociobehavioral interventions to strengthen effectiveness.	Padian et al. 2008
4.	Biomedical interventions are being offered in addition to an already relatively robust prevention package, including regular HIV testing, risk reduction counseling, latex condoms, and postexposure chemoprophylaxis.	Grant et al. 2010; Karim et al. 2010
5.	In most of the recently reported randomized controlled HIV prevention trials, there is some reduction in reported sexual risk over time and a lower than expected HIV incidence in the trial population overall, even when the modality under investigation has not shown any positive effect.	Padian et al. 2010

## BEHAVIORAL STRATEGIES

Efforts to modify sexual and drug-using human behaviors to reduce HIV risk have fallen short in the last 2 decades. Behavioral strategies have been defined as interventions to “motivate behavioral change in individuals and social units by use of a range of educational, motivational, peer-led, skill-building approaches as well as community normative approaches” (Coates and Gable 2008). A list of some available behavioral strategies is given in Table 3. The first successful examples of behavior change that led to decreased HIV transmission incidence were reported in men who have sex with men (MSM) (Winkelstein et al. 1988; Kippax and Race 2003). Subsequently, a number of countries have attributed decreases in HIV incidence to changes in sexual behavior, including Brazil, Cote d’Ivoire, Kenya, Uganda, Malawi, Tanzania, Zimbabwe, Burkino Faso, Namibia, and Swaziland (Stoneburner and Low-Beer 2004; Slutkin et al. 2006).

## Behavioral Intervention Research

The HIV literature is full of behavioral interventional and observational studies in a variety of settings and target groups, most of which have not objectively altered HIV transmission or acquisition rates. Seven randomized trials of behavioral interventions, described by Padian and colleagues, summarized in Table 4, showed neither benefit nor harm (Padian et al. 2010). Project EXPLORE is the only interventional study for HIV behavior with an HIV infection endpoint. Using a counseling intervention to reduce HIV incidence, the average follow-up was 3.25 yr and HIV acquisition was reduced by 18.2% in the experimental arm, but this effect compared with controls was insignificant. On more careful examination, there were more dramatic effects on HIV incidence in the first year (39%), but this effect was lost over time. There is a recurring theme in the literature that behavioral change is hard to maintain (Koblin et al. 2004; Karim et al. 2010).

L.-G. Bekker et al.

**Table 2.** Results of 40 randomized controlled trials reporting on 42 interventions to prevent sexual transmission of HIV

Type of intervention	HIV prevention efficacy			Total
	Positive effect (significantly reduced HIV incidence compared with control)	Adverse effect (significantly increased HIV incidence compared with control)	No effect (either way)	
Behavioral	–	–	7	7
Microfinance	–	–	1	1
Diaphragm	–	–	1	1
Vaginal microbicides	1	1	11	13
Preexposure prophylaxis	1	–	2	3
Male circumcision	3	–	1	4
Sexually transmitted infection (STI) treatment	1	–	8	9
Vaccine	1	–	3	4
Antiretroviral therapy (ART) in discordancy	1	–	–	1
Total	8	1	34	43

Data adapted from Padian 2010.

### Behavioral Intervention Programming

Auerbach and Coates (2008) state “behavioral strategies are necessary but not sufficient to reduce HIV transmission, but are essential in a comprehensive HIV prevention strategy. Behavioral strategies themselves need to be combinations of approaches at multiple levels of influence.” The list of possible behavioral interventions that have been identified over this time is long (Table 3), and inclusion of any component in a combination prevention package would depend on the target population and the risk activity.

The slogan, the “ABC of HIV prevention” was apparently first coined as part of a prevention campaign in Botswana in the late 1990s (Fig. 2). It was well known by then that individuals could reduce their risk of becoming HIV infected through sexual transmission; however, an “inappropriate and ineffective” emphasis on “abstinence only” in prevention programming was counterproductive in many settings where HIV risk occurred (Coates et al. 2008; Collins et al. 2008).

### The Need for Combination Prevention

Most forms of prevention need continual behavior modification to be effective. This effect was highlighted in two efficacy trials of preexposure prophylaxis (PrEP), one oral (Grant et al. 2010) and one topical (Karim et al. 2010). Both showed modest efficacy overall but improved efficacy in those participants who were most adherent. Future combination prevention packages are likely to contain one or more of these

**Table 3.** A list of some behavioral strategies

Sexual debut delay
Sexual partner reduction
Consistent condom usage
HIV counseling and testing
Sexual abstinence
Monogamy
Biomedical intervention uptake and consistent usage
Adherence to harm reduction strategies
Decreased substance use

Data adapted from Coates and Gable 2008.

**Table 4.** Randomized controlled trials assessing behavioral HIV prevention interventions

Author	Citation	Brief description of participants and study	Risk-taking behavior decreased during the study?	
			Intervention	Control
Kamali et al. 2003	Syndromic management of sexually transmitted infections and behaviour change interventions on transmission of HIV-1 in rural Uganda: A community randomised trial.	<b>Adults in rural Uganda</b> were randomized to syndromic STI management, behavioral interventions in combination with syndromic STI management and routine care and community development services. The primary outcome was HIV-1 incidence. Secondary outcomes were incidence of STIs and markers of behavioral change.	Yes	Yes
Koblin et al. 2004	Effects of a behavioural intervention to reduce acquisition of HIV infection among men who have sex with men: The EXPLORE randomised controlled study.	<b>Men that have sex with men.</b> The experimental intervention consisted of 10 one-on-one counseling sessions followed by maintenance sessions every 3 mo. Outcomes include HIV incidence and assessment of behavioral change, including occurrence of unprotected receptive anal intercourse with HIV-positive and unknown-status partners.	Yes	Yes
Ross et al. 2007	Biological and behavioral impact of an adolescent sexual health intervention in Tanzania: A community-randomized trial.	<b>Youth in Tanzania.</b> The intervention had four components: Community activities; teacher-led, peer-assisted sexual health education in years 5–7 of primary school; training and supervision of health workers to provide “youth-friendly” sexual health services; and peer condom social marketing versus standard activities. Impacts on HIV incidence, STI symptoms, as well as knowledge, reported attitudes, and other sexual health and behavioral outcomes were measured.	NA <sup>a</sup>	NA <sup>a</sup>
Corbett et al. 2007	HIV incidence during a cluster-randomized trial of two strategies providing voluntary counseling and testing at the workplace, Zimbabwe.	<b>Business employees in Zimbabwe.</b> Comparison of voluntary counseling and testing (VCT) when counseling and rapid testing were available onsite versus using prepaid vouchers for an external provider (which was the standard VCT). The main measured outcomes were rate of HIV incidence and VCT uptake.	NR	NR

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L.-G. Bekker et al.

**Table 4.** *Continued*

Author	Citation	Brief description of participants and study	Risk-taking behavior decreased during the study?	
			Intervention	Control
Jewkes et al. 2008	Impact of stepping stones on incidence of HIV and HSV-2 and sexual behaviour in rural South Africa: Cluster randomized controlled trial.	<b>Youth (15–26 yrs) in South Africa.</b> The intervention was Stepping Stones, a 50-h program that aims to improve sexual health by using participatory learning approaches to build knowledge, risk awareness, and communication skills and to stimulate critical reflection versus a 3-h intervention on HIV and safer sex. HIV and HSV-2 incidence, unwanted pregnancy, reported sexual practices, depression, and substance misuse were measured.	Yes	Yes
Patterson et al. 2008	Efficacy of a brief behavioral intervention to promote condom use among female sex workers in Tijuana and Ciudad Juarez, Mexico.	<b>Female sex workers living in Tijuana, Mexico</b> were provided with a 30-min behavioral intervention or a didactic control condition. At baseline and 6 mo, women underwent interviews and testing for HIV, syphilis, gonorrhea, and chlamydia.	Yes	Yes
Cowan et al. 2009	The Regai Dzive Shiri project: The results of a cluster randomized trial of a multi-component HIV prevention intervention for young people in rural Zimbabwe.	Youth—Community-based HIV prevention intervention for <b>adolescents</b> based in 30 communities <b>in rural Zimbabwe</b> . HIV and STI incidence, pregnancy, attitude, and self-reported sexual behavior were measured.	NR	NR

Data adapted from Padian et al. 2010.

NA, not available; NR, not recorded.

<sup>a</sup>Changes in behavior are not reported over time for this cohort as many of the participants were not sexually active at study enrollment.

biomedical interventions: vaginal microbicides providing a female-initiated methodology and oral PrEP as an alternative for those at risk for HIV exposures other than via the vaginal mucosa. Research is currently under way on rectal microbicides (Microbicide Trials Network 2011). The challenge will be to design prevention studies that embrace this integrated model of combined interventions. In addition, it will be important to monitor at the community level what happens when the combination intervention is scaled up (Piot et al. 2008).

## CONDOMS

Intact latex and polyurethane condoms have been shown *in vitro* to be impenetrable to particles the size of sexually transmitted pathogens (Lyle et al. 1997). When male condoms are used consistently, their effectiveness in reducing HIV transmission can be as high as 95% (Pinkerton et al. 1997). In most countries with generalized epidemics, condoms are actively promoted for all sexually active individuals as part of a comprehensive prevention approach despite





**Figure 2.** The “ABC” HIV prevention campaign. Billboard in Botswana. Sexual HIV risk could be avoided altogether by avoiding any sexual activities that could cause transmission of HIV (A, Abstain) or through avoiding sexual intercourse other than with a mutually faithful uninfected partner (B, Be faithful) or through the correct and consistent use of condoms (C, Condomise).

the social, economic, and psychological factors that limit their consistent use.

Several longitudinal cohort studies of sero-discordant couples estimated the effectiveness of male condoms for prevention of HIV transmission at around 85% (Weller et al. 2002). A study in MSM showed 76% efficacy in HIV prevention if used consistently (Golden 2006). The type of lubricant used, rather than strength of condom, was reported to be more important in safe usage of condoms in MSM (Harding et al. 2000). One of the most cited examples of how campaigns and policy can markedly increase male condom uptake is the much cited “100% condom use policy” in Thailand involving, in particular, the military and sex workers. Following an increase in condom usage from just over 10% in 1989 to >90% by 1993 in sex workers, incidence of new sexually transmitted infections (STIs) was seven times lower and HIV incidence was 50% lower (UNAIDS 2000). Similar success has been described in other female sex worker populations from other parts of the world (Weir et al. 1998).

Condom use and effectiveness at the population level is not well established. Demographic and health surveys from Latin America and Africa have reported increased usage of male condoms in recent years (Kerrigan et al. 2006; Shisana et al. 2009; Rehle et al. 2010). Recent encouraging reports suggest that the

use of mass media and creative condom social marketing to change attitudes and increase use have been successful (Foss et al. 2007).

### The Female Condom

Female condoms were developed to provide a female-controlled biomedical HIV prevention method. Also made from polyurethane or latex, they provide a physical barrier to HIV particles and prevent exposure to genital secretions containing HIV (Drew et al. 1990). No specific trials have been conducted to assess the efficacy of the female condom to prevent HIV infection, although impact on STI rates have been reported (French et al. 2003). Although the male partner is not unaware of the female condom, it does provide a prevention strategy that is less dependent on male willingness. Cost and mechanical difficulties have been cited as reasons for limited uptake (Galvao et al. 2005), but newer designs are easier to use, can be reused (Thomsen et al. 2006), and are made of materials that improve sensation with the promise of enhancing acceptability, uptake, and cost (Cofey et al. 2006). There are increasing reports of female condoms being used for HIV prevention in anal sex ([http://doh.dc.gov/doh/cwp/view,a,1371,q,602647,dohNav\\_GID,1839,dohNav,\[33815\],,asp](http://doh.dc.gov/doh/cwp/view,a,1371,q,602647,dohNav_GID,1839,dohNav,[33815],,asp)).

The perception exists that condom use indicates high-risk sexual partnerships associated

L.-G. Bekker et al.

with infidelity and infection. More than 2/3 of new infections occur in sub-Saharan Africa (SSA) between heterosexual cohabiting partners, and data from Rwanda and Zambia suggest that 60%–95% of new infections occur between married couples living together (Dunkle et al. 2008). In this setting, consistent condom use is challenging and couples-based HIV testing and counseling may have a greater role (The Voluntary HIV-1 Counseling and Testing Study Group 2000).

Additionally, there is a gap between supply and demand of condoms, especially in the developing world. Ideally, condoms should be free in these environments as research suggests even extremely low prices are a barrier to use (UNAIDS 2009). The United Nations Population Fund (UNFPA) estimated that at least 13.1 billion condoms are required annually to reduce the spread of HIV (UNFPA 2007). In 2008, <15% of this target was distributed globally.

### HIV COUNSELING AND TESTING

HIV counseling and testing (HCT) services are important entry points for prevention and care. Studies from different countries have shown that individuals take precautions to protect their partners once they know they are HIV positive (Sweat et al. 2000; Allen et al. 2003), and modeling studies have found HCT to offer substantial clinical benefits and to be cost effective even in settings where linkage and access to care is limited (Walensky et al. 2009).

The past decade has seen a rapid global scale-up of HCT (WHO 2009; Kranzer et al. 2010). HCT uptake is associated with a range of sociodemographic factors and identifying characteristics of individuals who have never been tested is important to develop services targeted at first-time testers and thus to achieve universal access to HCT (Khumalo-Sakutukwa et al. 2008; Helleringer et al. 2009).

Sexually active individuals in high HIV prevalence settings are at continuous risk of infection and should therefore be tested at regular intervals. The World Health Organization (WHO) recommends annual testing in these settings, and a recent study from South Africa

found annual screening to be very cost effective even in the Western Cape, the province with the lowest rates of HIV infection in South Africa (Walensky et al. 2009).

### Evidence for HCT Role in Prevention

Studies have shown that many infected persons decrease high-risk sexual or needle-sharing behaviors once they are aware of their positive HIV status. The majority of this research is from high-income countries, with the strongest evidence for behavior change within discordant couples who also received counseling. Most studies that have assessed the effect of HCT on sexual behavior have focused on the change in behavior over periods of less than a year (Denison et al. 2008).

The challenge is to increase testing coverage and identify those who are positive for care (Kranzer et al. 2010). Strategies to increase testing have included national campaigns, provider-initiated counseling such as has been implemented in Botswana (Bateganya et al. 2007), couples counseling services, and community-level campaigns such as Project Accept (Fig. 3) (Khumalo-Sakutukwa et al. 2008). These alternative strategies not only increase coverage but ensure inaccessible populations such as men, the working population, and asymptomatic HIV-infected individuals are also tested (Matovu and Makumbi 2007). The role of incentives to increase testing coverage is also being investigated in a number of settings and populations (<http://www.cgdev.org/content/publications/detail/1424161>).

### PREVENTION WITH POSITIVES

Traditional prevention has been thought of as protecting individuals from becoming HIV infected. Positive prevention embraces the concept that individuals who have tested positive may be helped to avoid spreading the infection further. Positive prevention also recognizes that infected individuals may want to remain sexually active and may wish to have children, both of which can be done with minimized harm to others (PEPFAR Prevention 2008).





**Figure 3.** Testing coverage can be markedly increased by using a variety of non-traditional venues and outlets such as household campaigns, high-risk venues, work environments, and community-based mobile testing units such as The Tutu Tester is a mobile testing service operating in Cape Town, South Africa (van Schaik et al. 2010).



### Research in Positive Prevention

Antiretroviral therapy (ART) has dramatically reduced the morbidity and mortality of HIV infection through sustained reduction in HIV viral replication (De Cock et al. 2009). This reduction in HIV viral load (plasma HIV ribonucleic acid [RNA] levels) reduces infectiousness in the infected individual and, as a result, susceptibility for the noninfected partner (Musicco et al. 1994).

### Evidence for Reduced HIV Transmission

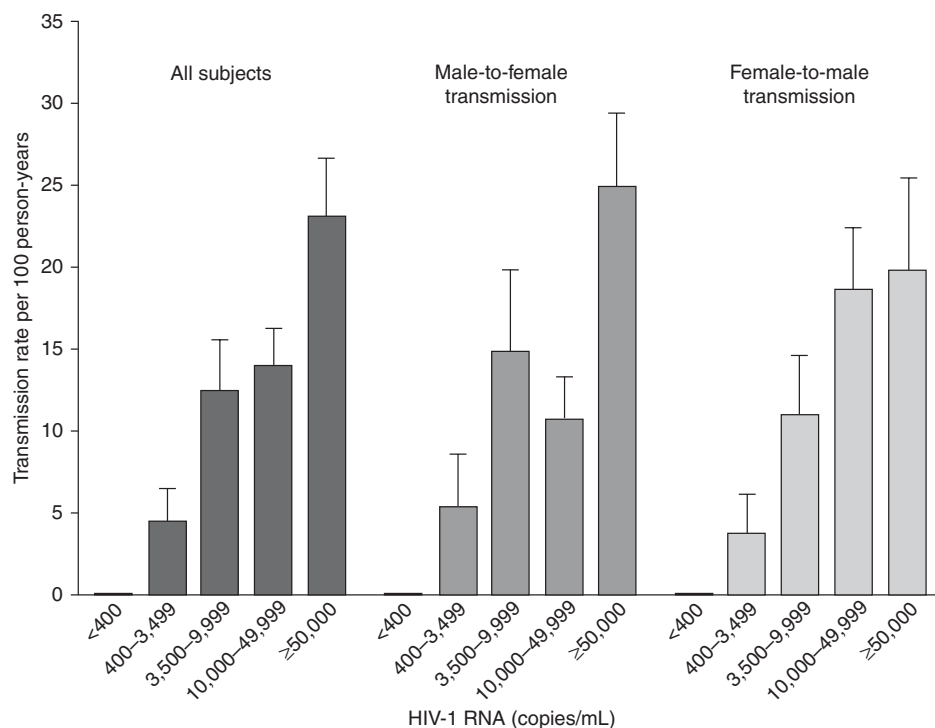
Viral load is the single greatest risk factor for all transmission modes. ART can reduce the plasma and genital HIV viral load in the infected individual to undetectable levels (Grulich et al. 2010). In a study of 415 HIV serodiscordant couples in Uganda, 21.7% of the initially uninfected partners became infected over 30 months of follow-up, translating to a transmission rate of approximately 12 infections per 100 person years (Fig. 4) (Quinn et al. 2000). No transmission events occurred in those couples in which the infected partner had a plasma HIV-1 RNA level of less than 1500 copies/mL, and the transmission risk increased as plasma HIV-1 RNA levels increased. For every 10-fold increase in viral load, there was a greater than twofold risk of transmission. This was similarly shown in HIV-serodiscordant couples in Zambia (Fideli et al. 2001). Plasma HIV-1 RNA levels generally

correlate positively with the concentration of HIV in genital secretions, rectal mucosa, and saliva, although inflammation can stimulate local replication (Cu-Uvin et al. 2000; Lampinen et al. 2000; Shugars et al. 2000). Other studies have shown that transmission events may be observed at a very low plasma HIV-1 RNA level, suggesting that plasma viral load is not the only determinant of transmission (Vernazza et al. 2000; Tovanabutra et al. 2002).

### Clinical Research in Discordant Couples

The outcomes of two retrospective clinical studies that showed the benefit of ART on HIV transmission (Musicco et al. 1994; Castilla et al. 2005) have been corroborated by the recent release of early results from a randomized trial, known as HPTN 052. The deferred treatment study arm was prematurely halted after a scheduled interim review by an independent Data and Safety Monitoring Board (DSMB) that concluded that initiation of ART by HIV-infected individuals substantially protected their HIV-uninfected sexual partners from acquiring HIV infection, with a 96% reduction in risk of HIV transmission. The study enrolled 1763, mostly heterosexual discordant couples in which the infected index case was ART-naïve and had a CD4 T-cell count of 350–550 cells/mm<sup>3</sup>. Treatment was commenced at 250 cells/mm<sup>3</sup> in the control or “treatment deferment” arm (Cohen et al. 2011).

L.-G. Bekker et al.



**Figure 4.** HIV transmission is dependent on plasma viral load. Mean (+SE) rate of heterosexual transmission of HIV-1 among 415 couples, according to the sex and the serum HIV-1 RNA level of the HIV-1-positive partner (Quinn et al. 2000). At baseline, among the 415 couples, 228 male partners and 187 female partners were HIV-1-positive. The limit of detection of the assay was 400 HIV-1 RNA copies per milliliter. For partners with fewer than 400 HIV-1 RNA copies per milliliter, there were zero transmissions.

### Mathematical Models and Population-Level Impact

Extrapolating from this result, reduction of viral load within a population would likely lower the rate of heterosexual transmission within that population. Substantial reduction in the number of anticipated HIV cases in concentrated epidemics of injection drug users and MSM have been reported in at least two population-based studies of HIV incidence before and after the availability of ART (Katz et al. 2002; Fang et al. 2004; Porco et al. 2004). Mathematical models have been used to predict the ability of HIV treatment to reduce HIV incidence and prevalence. In a model generated by Gray et al. from the Ugandan transmission study data, ART would be predicted to reduce incident HIV by 80% (Gray et al. 2001). Conversely, others

have argued that ART could not reduce HIV prevalence in resource-constrained regions (Baggaley et al. 2006). More recently, this has led to the concept of “Test and Treat,” modeled by Granich et al. (2009), which espouses universal HIV testing with immediate commencement of ART, regardless of clinical or immune status. This controversial model, based on the South African epidemic, with annual testing, heterosexual transmission, and a number of other assumptions, reported that immediate ART initiation could reduce HIV incidence by 95% over a 10-year period. To be considered, of course, are the cost and operational challenges as well as the risk of drug resistance and toxicity (Padian et al. 2008).

However, this shift from a focus on downstream therapeutic application of ART to more upstream preventive benefits of eliminating

HIV transmission has received considerable interest. A number of community-based feasibility studies are under way or planned in the United States and Southern Africa, and it is envisaged that definitive randomized trials will be designed and executed in the next 5–10 years.

### MALE CIRCUMCISION

Practiced since at least the Sixth Dynasty (2345–2181 B.C.), approximately 30%–34% of adult men globally are circumcised (Padian et al. 2008). Male circumcision was first proposed in 1986 as an intervention to reduce risk of HIV acquisition (Fink 1986). Ecological and observational studies had shown that, in regions where HIV transmission is predominantly heterosexual, the prevalence of HIV and of male circumcision are inversely correlated (Bailey et al. 2001). The prevalence of HIV has been shown to be significantly higher in uncircumcised than in circumcised men in more than 30 cross-sectional studies, and a number of prospective studies have shown a protective effect, ranging from 48% to 88% (Bongaarts et al. 1989; Moses et al. 1990; Caldwell and Caldwell 1996; Gray et al. 2000; Reynolds et al. 2004; Buchbinder et al. 2005). A meta-analysis of studies from SSA reported an adjusted relative risk of 0.42 (95% CI 0.34–0.54) in all circumcised men, with a stronger adjusted relative risk of 0.29 (0.20–0.41) in circumcised men who were at higher risk of acquiring HIV (Weiss et al. 2000).

### RCTs

To definitively document the protective associations of circumcision, three RCTs were designed and undertaken in three sub-Saharan countries: South Africa, Kenya, and Uganda. Design and results are presented (Table 5). A total of 11,054 HIV-negative men aged between 15 and 49 yr were randomized and similar to the observational data estimates, the summary rate ratio was 0.42 or a protective effect of 58% (Padian et al. 2010). Unlike many other biomedical interventions, male circumcision is a one-time procedure for which adherence issues are limited to refraining from intercourse

during healing (Padian et al. 2010). As a result of these three randomized controlled clinical trials, WHO and UNAIDS (2007) have now made strong recommendations to roll out male circumcision with all possible urgency. Most recent long-term follow-up from these studies indicate that efficacy does not decrease with time, suggesting that the long-term efficacy of the intervention outweighs any risk compensation should this phenomenon be occurring (Kong et al. 2011).

### MC to Prevent Male-to-Male HIV Transmission

Observational studies of MC to reduce HIV transmission between MSM have shown inconsistent results perhaps because men may adopt both receptive and insertive sexual roles. In a cohort study of HIV-negative MSM, no association between circumcision status and HIV acquisition was shown (Grulich et al. 2001). It is unclear what role MC would have in bisexual men.

### MC to Prevent Male-to-Female HIV Transmission

A previous observational study in HIV-discordant couples in Rakai suggested a lower rate of male-to-female HIV transmission from circumcised HIV-infected men, particularly if their viral load was below 50,000 copies per mL (Gray et al. 2000). A fourth prospective randomized controlled trial was conducted in discordant couples and examined HIV transmission to female partners of HIV-infected men in Rakai, Uganda (Table 4). The study was stopped prematurely for futility; however, HIV acquisition was increased in the subgroup of female partners of men who resumed sexual activity early before complete wound healing (relative risk: 2.92, 95% CI 1.02–8.46,  $P = 0.06$ ).

### Biological Explanation

There are a number of biological studies that suggest plausible mechanisms for the protection offered by removal of the male foreskin. These are summarized in Table 6.

L.-G. Bekker et al.

**Table 5.** Randomized trials of male circumcision (MC) to prevent HIV transmission

Country	Funding	Study population	Design/question/ method	Outcome	Reference
South Africa	Agence Nationale de Recherche sur le Sida (ANRS)/ National Institute for Communicable Diseases (South Africa)	3274 18- to 24-yr-old men in a semiurban, informal settlement called Orange Farm	Does circumcision reduce male risk of HIV infection by female partners? Study visits at months 3, 12, 21 postrandomization; circumcision performed using the sleeve method.  Both the intervention and the control group received an enhanced prevention package beyond the local standard of care.	Stopped early. MC reduced the risk of HIV infection by 60%–61%.	Auvert et al. 2005
Uganda	National Institutes of Health/Johns Hopkins University, Rakai Health Sciences Project	Approximately 5000 15- to 49-yr-old men in rural Uganda (Rakai District)	Does circumcision reduce male risk of HIV infection by female partners? Four visits over 2 yr of follow-up; circumcision performed using the sleeve method.  Both the intervention and the control group received an enhanced prevention package beyond the local standard of care.	Stopped early. MC reduced the risk of HIV infection by 48%.	Gray et al. 2007
Kenya	National Institutes of Health and Canadian Institute of Health Research/ University of Nairobi, University of Manitoba	2784 18- to 24-yr-old urban HIV-negative men	Does circumcision reduce male risk of HIV infection by female partners? Six study visits (months 1, 3, 6, 12, 18, 24) over 2 yr; circumcision performed by forceps-guided method.  Both the intervention and the control group received an enhanced prevention package beyond the local standard of care.	Stopped early. MC reduced the risk of HIV infection by 53%.	Bailey et al. 2007

*Continued*

**Table 5.** *Continued*

Country	Funding	Study population	Design/question/ method	Outcome	Reference
Uganda	Bill and Melinda Gates Foundation/ Johns Hopkins University, Rakai Health Sciences Project	200 men had been enrolled concurrently with female partners and had couples HCT. In some, the women were enrolled separately	Is circumcision safe for HIV-positive men? How does it affect rates of acquisition of STIs? Does circumcision reduce female risk of infection by HIV-positive, circumcised male partners? Four visits over 2 yr of follow-up; sleeve method.	Trial suspended: DSMB review determined that the study lacked statistical power to answer its study question.	Wawer et al. 2009

Data from AVAC 2007 and Padian et al. 2010.

**Other Benefits**

The Rakai MC circumcision study conducted in 2005 also reported that men circumcised at the beginning of the study had a 50% reduction in rates of genital ulcer disease (GUD), attributable to herpes, syphilis, and chancroid, a reduction in acquisition of genital herpes (27%), and a 30%–35% reduction in rates of human papillomavirus (HPV), including the types that cause cancer. Benefits also extended to the female partners of the circumcised men: a 50% reduction in rates of GUD, as well as a dramatic reduction in trichomoniasis, HPV infection, and bacterial vaginosis (Bailey et al. 2001;

Weis et al. 2006). HIV-infected men may also experience less GUD (Schneider et al. 2010).

**Current Implementation Programs**

Although the efficacy of MC on reducing individual risk is clear, the population-level effectiveness of this procedure in reducing HIV transmission will depend heavily on the acceptability of male circumcision programs in specific populations (Westercamp and Bailey 2007). Data on its acceptability among adults show this is likely to be highly context-specific and influenced by local cultural norms and practices (Eaton and Kalichman 2009).

**Table 6.** Some biological reasons for the protection against HIV acquisition in men undergoing male circumcision

Explanation	Reference(s)
1. The inner mucosal surface of the human foreskin, exposed on erection, has nine times higher density of HIV target cells (Langerhans' cells, CD4 <sup>+</sup> T cells, and macrophages) than does cervical tissue.	Patterson et al. 2002
2. The foreskin's inner surface lacks the protective layer of squamous epithelial cell HIV target cells found on the outer surface and the glans.	McCoombe and Short 2006
3. In explant culture, several times more HIV is taken up by Langerhans' cells and CD4 <sup>+</sup> T cells in foreskin than in cervical tissue.	Patterson et al. 2002
4. A foreskin is associated with increased incidence of ulcerative sexually transmitted infections; the number of HIV target cells in the prepuce is increased in the setting of recent STIs.	Weis et al. 2006; Bailey et al. 2001; Donoval et al. 2006
5. Susceptibility of the foreskin to abrasions.	



L.-G. Bekker et al.

## STI INTERVENTIONS

Longitudinal studies have shown substantial relative risks for HIV infection associated with various STIs with syphilis, chancroid, and genital herpes having larger effects on susceptibility than gonorrhea, chlamydia, and trichomonas (Stamm et al. 1988; Rottingen et al. 2001). These ulcerative diseases appear to create an entry point for the virus by disrupting the genital epithelial barrier leading to a greater susceptibility (Ghys et al. 1997). In addition, studies have shown that HIV viral shedding in the genital tract is substantially increased with a sexually transmitted coinfection, and this replication is reduced after treatment of the STI (Eron et al. 1996).

As a result, efforts to ensure prompt diagnosis and treatment of STIs along with behavioral risk reduction have been part of HIV prevention programming since the 1980s. In 1989, Pepin and colleagues suggested that the interaction of HIV and STIs may present an opportunity for intervention (Pepin et al. 1989). Empirical evidence for this intervention has included uncontrolled intervention studies among sex workers and community-based RCTs in general populations (Laga et al. 1994).

## Clinical Trials of STI Treatment

Eight of the nine RCTs of STI treatment for HIV prevention showed no effect, although one additional study found a significant reduction on HIV incidence in a subgroup of men who attended program meetings (Table 7) (Gregson et al. 2007). Four community-randomized trials have been conducted to assess the effect on HIV transmission and HIV acquisition through reduction of the incidence of the most common curable STIs. Of all four study outcomes, only the Mwanza trial reported significant reduction (38%) in HIV incidence. Many possible reasons for this discrepancy have been cited but most compelling are the differences between the stage of the epidemic in Uganda and Tanzania when the studies were performed. The epidemic in Uganda was more established (HIV prevalence 16% and stable) with lower risk behavior and

lower rates of curable STIs. In contrast, the HIV prevalence in Mwanza was 4% and rising with much greater rates of STIs (Grosskurth et al. 2000).

These data would suggest that STI treatment interventions can have an impact where treatable STIs are prevalent and where HIV incidence is very high in the general populations. However, even if the HIV epidemic has matured in the general adult population, adolescents as they sexually debut may initially have low HIV prevalence and constitute a population where STI control may be very important. It is still recommended that STI treatment should be an essential component of HIV control programs in communities in which the burden of STIs is substantial (Grosskurth et al. 2000; Hayes et al. 2010).

## Herpes Simplex 2 and HIV Transmission

In SSA, HSV-2 infections have a two- to three-fold increased effect on HIV acquisition in the general population (Freeman et al. 2006). Initial proof of concept, randomized trials of suppressive treatment with valaciclovir reported reduced HIV shedding in genital secretions of coinfecting individuals, suggesting potential for reduced HIV transmission risk (Nagot et al. 2007; Zuckerman et al. 2007). Subsequently, in three RCTs, antivirals for herpes simplex virus (HSV) suppression were insufficiently potent to alleviate persistent genital inflammation in HIV-negative HSV2-positive persons, and the reduction in HIV levels in HIV-positive persons was insufficient to reduce HIV transmission (Table 7) (Hayes et al. 2010).

## HIV PREVENTION AMONG INJECTING DRUG USERS

HIV prevention for people who inject drugs (commonly referred to as injecting drug users, or IDUs) presents a difficult paradox. There is abundant evidence for the efficacy of a number of interventions for this population, and clear and compelling data has emerged on the efficacy of combinations of these interventions in



**Table 7.** The randomized trials of treatment of STIs to reduce HIV transmission

Intervention	Country/region	Target population and annual HIV incidence (ppy)	Efficacy/outcome	Reference
Individual syndromic STI <sup>a</sup> treatment to reduce HIV incidence (CRCT)	Mwanza, Tanzania	General population; 0.9%	38% reduction in HIV incidence	Grosskurth et al. 2000
STI therapy <sup>b</sup> to reduce HIV incidence (everyone treated every 10 mo) (CRCT)	Rakai, Uganda	General population; 1.5 ppy	Nil	Wawer et al. 2009
Individual RCT of intensive, microscopy-assisted STI <sup>a</sup> screening and treatment to reduce HIV incidence		FSW; 7.6 ppy	Nil	Ghys et al. 1997
Individual syndromic STI <sup>b</sup> to reduce HIV incidence (CRCT)	Masaka, (rural) Uganda	General population; 0.8 ppy	Nil	Kamali et al. 2003
Treatable STI <sup>a</sup> periodic presumptive therapy Individual RCT	Kenya	FSW; 3.2 ppy	Nil	Kaul et al. 2004
Individual syndromic STI treatment <sup>a</sup> to reduce HIV incidence (CRCT)	Manicaland, Zimbabwe	General population; 1.5 ppy	Nil; subgroup of men who attended program meetings (IRR 0.48; $p = 0.04$ )	Gregson et al. 2007
HSV-2 suppression <sup>c</sup>	Tanzania	HSV-2-positive women; 4.1 ppy	Nil	Watson-Jones et al. 2008
HSV-2 suppression <sup>c</sup>	Africa; Peru and United States	WSM; MSM HSV2 seropositive; 3.3 ppy	Nil (some benefit in subset of women who took >90% of doses)	Celum et al. 2008
HSV-2 suppression <sup>c</sup>	Africa	HIV/HSV-2 positive; 2.7 ppy	Nil	Celum et al. 2010

ppy, per hundred person years or annual percentage; CRCT, community randomized control trial; FSW, female sex workers; HSV-2, herpes simplex virus 2; IRR, incidence rate ratio; WSM; women who have sex with men.

<sup>a</sup>Treatable STIs: Chancroid, syphilis, gonorrhea, chlamydial infections, and trichomonas.

<sup>b</sup>Single-dose oral antibiotic.

<sup>c</sup>Acyclovir treatment.

achieving control of HIV spread via this route (Degenhardt et al. 2010). Yet IDU remain the least served of any risk group globally for prevention, treatment, and care (Wolfe et al. 2010). Epidemics driven by IDU risks and by risk-enhancing structural and policy environments continue to expand in 2010 (Beyrer et al. 2010). These policy failures include punitive and repressive drug laws, criminalization of drug dependency and possession, and the continued resistance

to the provision of evidence-based drug treatment, including methadone maintenance therapy in many states and regions (Strathdee et al. 2010).

HIV spread among IDUs has been driven largely, but not exclusively, by injecting use of heroin. Cocaine, methamphetamine, and combinations are also important substances associated with injecting risks. Heroin predominates in Eastern Europe and Central Asia, North, South, and Southeast Asia, and Western Europe,

L.-G. Bekker et al.

encompassing the major populations at risk for HIV through injecting (Mathers et al. 2008). The most recent global estimate, from the reference group to the United Nations on HIV and injecting drug use was that some 15.9 million persons (range from 11.0 to 21.2 million) worldwide were IDU in 2007 (Beyrer 2010).

### Evidence for Efficacy

The literature on HIV prevention for this population is large and growing (Degenhardt et al. 2010). The most compelling recent data suggest, as with prevention of sexual transmission, that no single intervention alone can reduce HIV risks enough to control injecting-driven epidemics. Encouragingly, however, recent modeling studies show that combination approaches to HIV prevention for this population can be synergistic in effect and have real impact on HIV risks at individual, couple, network, and population levels of spread (Degenhardt et al. 2010).

The components of effective prevention services for IDU include individual and higher-level interventions (Table 8). An essential component is access to safe injecting equipment. Because the primary risk for HIV acquisition and transmission among drug users is the reuse of contaminated injecting equipment, multiple approaches to reducing equipment reuse,

termed needle and syringe exchange programs (NSP), have been developed. The provision of equipment for people who inject has proven politically challenging in many contexts, because this has been seen (based on no empirical evidence) as “encouraging” injecting. Indeed, the U.S. federal ban on funding for such programs, lifted in 2010 by the Obama administration, was based on this unsound premise (Beyrer et al. 2010). A recent global review and modeling exercise of the evidence for efficacy suggests that with high coverage, NSP can reduce HIV incidence at population levels by 20% over 5 years, but the reduction is too modest to control HIV spread (Degenhardt et al. 2010).

A second critical component of HIV prevention for IDU is drug treatment. The first agent shown to have efficacy in reduction of HIV transmission among drug users was methadone (Metzger et al. 1999). Because methadone is an oral administered liquid and an opiate agonist, opioid-dependent patients can be maintained on the agent and reduce dramatically their injecting drug use. This simple “substitution” therapy, as it has come to be known, was shown by Metzger and colleagues (1999) to markedly reduce HIV infection rates among IDU in Philadelphia in the 1990s. Newer agents are also now available, but there have been significant obstacles to the

**Table 8.** Structural interventions associated with prevention in injection drug use

Level	Physical environment	Social environment	Economic environment	Policy environment
Micro	Unsafe drug use, injecting, and sex work locations Injecting in public places Detention centers	Social and peer group risk norms Policing and crackdowns Lack of health and welfare services	Cost of living and health services Cost of prevention services Lack of income-generation opportunities	Access to clean needles and syringes Policy and programs for distribution Housing access
Macro	Drug traffic and distribution routes Population mobility	Sex inequalities and risk Stigmatization and marginalization of IDU Inadequate public advocacy	Reduced public spending Increase in informal income generation Economic uncertainty	Laws governing human rights Laws governing drug possession Public health policy and harm-reduction services

Data adapted from Degenhardt et al. 2010.

widespread use of these agents. Methadone was strongly opposed by the Soviet Union when it was first introduced, and opioid substitution therapy (OST) remains illegal in Russia (Beyrer et al. 2010).

Although NSP and OST in combination can reduce HIV risks, recent modeling work by Hallett et al., reported by Degenhardt et al. (2010), showed that a third element is essential for individuals and for epidemics: access to antiretroviral therapies (ARVs). ARV access for IDUs alone had roughly the same impact on HIV incidence as the combination of OST and NSP, and was significantly higher when ARVs were available to HIV-infected IDU at higher (<350 CD4s) levels. They found a dramatic synergistic impact of provision of NSP, OST, and ARV on reducing HIV incidence over time, with a 39% reduction in population levels of HIV infection over 5 years with the combination approach (Degenhardt et al. 2010). This model assumed quite modest levels of efficacy for each component at the individual level (60% for OST, 40% for NSP, and 90% for ARVs when initiated at the higher CD4 level) (Degenhardt et al. 2010).

### Challenges and Opportunities for Implementation

Although it is tremendously encouraging to show the synergistic effects of combined preventive interventions on HIV incidence at population levels among IDUs, the realities of access to care for this population are sobering. Wolfe et al. reviewed access to care for IDUs in selected high-burden countries and found that among all populations at risk for HIV infection, IDUs remained the least served (Wolfe et al. 2010). An even more telling finding was that in China and Vietnam, the number of drug users in detention is three times and 33 times higher, respectively, than those in treatment. Incarceration is not an evidence-based approach to HIV prevention, but rather a well-described risk for HIV infection among drug users (Beyrer et al. 2010).

Strathdee et al. used the risk-environment framework to investigate another aspect of IDU risks that poses real challenges—the social,

policy, and legal environments that can reduce, or *drive*, HIV risks (Strathdee et al. 2010). They found that structural aspects of risk environments had substantial impacts on HIV risks and disease spread. As IDU risks emerge in new settings, as was happening in East and South Africa in 2010, these challenges are likely to continue to undermine our responses (Beyrer et al. 2010).

### STRUCTURAL APPROACHES TO HIV PREVENTION

Structural factors in HIV epidemics are defined as “physical, social, political, cultural, organizational, community, economic, legal, or policy aspects of the environment that facilitate or obstruct efforts to avoid HIV infection” (Gupta et al. 2008). Structural interventions are programs or policies that seek to address these factors and prevent HIV acquisition through altering the context and mechanisms by which the behavior occurs rather than targeting the behavior itself (Gupta et al. 2008).

### Evidence Linking Structural Factors to HIV

The literature cites both indirect associations, such as increased HIV vulnerability among orphaned or homeless children (Hallman 2005), and more direct associations, such as studies on migration linking South African mine workers and their high-risk work conditions plus separation from family to unprotected sex with prostitutes (Lurie et al. 2003). Associations, however, are not always clear-cut: Although poverty has been linked to HIV vulnerability, in a study of household wealth and HIV prevalence in population-based surveys in SSA, HIV prevalence was highest in the wealthier sector of the population in six of the eight surveys studied (Sumartojo et al. 2000; Hallman 2005).

### Examples of Structural Approaches in HIV Prevention

Structural approaches may be single policies or programs (revoking a discriminatory law, e.g., the South African sodomy law in 1994)

L.-G. Bekker et al.

or transformational processes (community mobilization for MC in KwaZulu Natal following King Goodwill's pronouncement that Zulu men should be circumcised). Their common purpose is to change the social, economic, political, or environmental factors that determine HIV risk and vulnerability in specific settings (Gupta et al. 2008). The policy and legal shifts that enabled NSP and OST to operate for IDUs is an example of a successful structural intervention (Drucker et al. 1998).

Within the social framework, school retention has been linked to a lower HIV acquisition risk. This effect may be caused by reducing child prostitution, child labor, and antisocial behavior as well as opportunities for HIV and sex education (Hallman 2006). A higher level of education is associated with safer sexual practices and a later sexual debut (Prata et al. 2005), yet school fees are a major barrier to school attendance in the developing world.

One of the ways economic frameworks create a risk environment for HIV is through women's financial dependency on men and the lack of opportunities for both sexes in the developing world. Microcredit programs, for example, may reduce women's HIV vulnerability by strengthening their economic options (Hargreaves et al. 2002; Hall 2006).

### Designing Structural Interventions and Their Evaluation

This effort requires an analysis of social, political, economic, and environmental factors in a given setting that increase risk or vulnerability. Different factors may have more than one causal pathway from the structural factor to the behavior(s) that need to change to reduce risk (Over 1998).

A review of 24 IDU harm reduction programs in 1989 found prevention efficacy for such programs without associated adverse events. Further structural interventions to reduce some legal limitations, increase community and social mobilization, and upscale such programs holds great potential for reducing HIV vulnerabilities among IDUs (Table 7) (Degenhardt et al. 2010). Some successful

structural interventions have occurred at the country or district level. The Mbeya region in Tanzania is one of the most affected regions in the country but reported a 7% decrease in HIV prevalence over a few years. The intervention included a single regional HIV plan with political support, regional AIDS coordination, and involvement of business and nongovernmental organizations (NGOs) (Vogel 2007).

It is possible that individuals will find it difficult to change their behavior in relation to HIV risk until they have a stronger social, political, economic, and environmental framework in which to live their lives. As a result, structural approaches that are context-specific and evidence-based should be a part of an overall HIV prevention package that includes behavioral and biomedical approaches (Gupta et al. 2008).

### CONCLUSION

The aim of the Sixth Millennium Development Goal is to halt, and reverse, the spread of HIV by 2015. This article describes an impressive array of evidence-based devices (condoms, harm reduction, MC) that can be implemented along with information, skills, and services. Concerted HIV prevention efforts from countries as diverse as Thailand, Australia, and Senegal have resulted in maintenance of low seroprevalence rates (Winkelstein et al. 1987; Kippax et al. 2003). Other studies conducted in high-risk populations have shown that HIV prevention can work, even in the most challenging settings. Yet, despite this, UNAIDS tells us that only 60% of sex workers, 46% of injection drug users, and 40% of MSM were reached with HIV prevention programs in 2008 (UNAIDS 2008). The positive results of biomedical interventions in 2010 and those expected over the next several years give promise that a number of other interventions can be added to the menu. The era is one of HARP-targeted, strategic, and creative combinations of behavioral, biomedical, and structural interventions. These programs will require universal access, wide-scale implementation, careful monitoring, and evaluation, financial, and technical resources

and robust commitment at regional and country levels (Coates et al. 2008; Merson et al. 2008). We may then begin to see a substantial impact on the spread of HIV globally.

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L.-G. Bekker et al.

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L.-G. Bekker et al.



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