NEW APPROACHES TO HIV PREVENTION

ACCELERATING RESEARCH AND ENSURING FUTURE ACCESS

GLOBAL HIV PREVENTION WORKING GROUP

AUGUST 2006

ABOUT THE GLOBAL HIV PREVENTION WORKING GROUP

The Global HIV Prevention Working Group is a panel of 50 leading public health experts, clinicians, biomedical and behavioral researchers, and people affected by HIV/AIDS, convened by the Bill & Melinda Gates Foundation and the Henry J. Kaiser Family Foundation. The Working Group seeks to inform global policy-making, program planning, and donor decisions on HIV prevention, and to advocate for a comprehensive response to HIV/AIDS that integrates prevention, treatment, and care. Working Group publications are available at www.gatesfoundation.org and www.kff.org.

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ACCELERATING RESEARCH AND ENSURING FUTURE ACCESS

FEATURES AND CHARTS

EXECUTIVE SUMMARY

ABOUT THIS REPORT

A growing number of promising new HIV prevention approaches are in the late stages of clinical research, and have the potential to dramatically reduce the burden of HIV/AIDS around the world. Research on some of these approaches, such as male circumcision and diaphragms, could show results within the next two years.

But there are serious obstacles that could significantly delay, or even derail, critical prevention trials—including inadequate resources and capacity to launch and complete trials, and emerging ethical concerns. Moreover, the world is unprepared to capitalize on the potential success of prevention research currently underway. Very little has been done to mobilize resources and develop the public health guidance, provider training, and public education needed to ensure rapid implementation of new prevention methods.

This new report by the Global HIV Prevention Working Group, *New Approaches to HIV Prevention: Accelerating Research and Ensuring Future Access*, summarizes the state of HIV prevention research, and makes recommendations to speed research on promising new HIV prevention methods, and ensure rapid access to new tools and strategies as soon as they are proven effective.

Twenty-five years into the global HIV/AIDS epidemic, HIV infection rates are alarmingly high, and more than 4 million people become infected every year.[1] Despite the proven effectiveness of existing prevention approaches, fewer than one in five people at high risk for HIV have access, and current prevention approaches are not practical for everyone, especially women. New approaches to HIV prevention are urgently needed.

This Global HIV Prevention Working Group report addresses three critical areas:

1. HIV Prevention Research: State of the Science

A wide range of promising new HIV prevention approaches are being tested in clinical trials, including male circumcision, cervical barriers, pre-exposure prophylaxis with antiretroviral drugs, herpes suppression, microbicides, and HIV vaccines. The results of some of these studies could be available within the next two years.

2. Accelerating HIV Prevention Research

Prevention research faces serious challenges that could delay the completion of critical trials, or prevent planned trials from moving forward—including a lack of adequate research infrastructure in developing countries, limited resources, emerging ethical concerns, and inadequate community engagement.

3. Preparing for Access

Despite the fact that some new HIV prevention methods could be shown to be effective in the near future, virtually no planning or resources have been dedicated to ensuring future access to new prevention approaches. Key implementation issues that must be addressed immediately include ensuring adequate resources, developing public health guidelines, providing health care worker training, and ensuring that risk behavior does not inadvertently increase with the introduction of new prevention methods.

Unless the world acts now to accelerate HIV prevention research and prepare for implementation of effective new approaches, we risk letting new prevention methods sit idle while 4 million people become infected every year. Averting that fate is the goal of this report, and should be a top priority in the fight against HIV/AIDS.

No "Magic Bullet" for HIV

It is critical to note that there is no "magic bullet" for HIV prevention. None of the new prevention methods currently being tested is likely to be 100 percent effective, and all will need to be used in combination with existing prevention approaches if they are to reduce the global burden of HIV/AIDS.

SUMMARY OF FINDINGS AND RECOMMENDATIONS

I. HIV PREVENTION RESEARCH: STATE OF THE SCIENCE

A wide range of promising HIV prevention approaches are in late-stage clinical trials:

- **Male circumcision:** Researchers have long observed that countries with higher rates of male circumcision have lower rates of HIV infection. In 2005, the first randomized efficacy trial of male circumcision for HIV prevention, conducted in South Africa, showed that circumcised men were 60 percent less likely than uncircumcised men to become infected with HIV from female partners.

  Three additional efficacy trials of male circumcision are underway in Kenya and Uganda to assess the applicability of the South African findings in other settings and populations, and to determine if male circumcision also reduces the risk of HIV transmission from men to their female partners. Results are expected in 2007.

- **Cervical barriers:** Researchers hypothesize that cervical barriers such as diaphragms, which are currently used for contraception, may help protect women from HIV and other sexually transmitted diseases. An efficacy trial of the diaphragm for HIV prevention is nearing completion in South Africa and Zimbabwe, and results are expected in 2007.

- **Pre-exposure prophylaxis with antiretrovirals:** Research in animals suggests that antiretroviral drugs used for HIV treatment may also be effective at preventing infection in HIV-uninfected adults, an approach called pre-exposure prophylaxis, or PREP. Efficacy trials of this approach are underway in Botswana, Peru, and Thailand. Results could be available as early as 2007 or 2008.

- **Herpes suppression:** Herpes, which infects up to 70 percent of people in some parts of sub-Saharan Africa, can triple the risk of HIV acquisition, as well as increase the risk of transmission to others. The inexpensive, off-patent drug acyclovir is approved for herpes suppression, and two trials are being conducted in Africa, Latin America, and the U.S. to test the efficacy of suppressing herpes to lower HIV risk. Results are expected in 2007 and 2008.

- **Microbicides:** Microbicides are topical substances, such as gels or creams, that could be applied to the vagina or rectum to reduce HIV transmission. Five first-generation vaginal microbicide candidates are currently in late-stage clinical trials; results from some of these trials could be available by 2008. In addition, a number of second-generation microbicide candidates—which specifically target HIV or molecules of the cells it infects—are in earlier stages of research, and could complete clinical trials within 10 years.

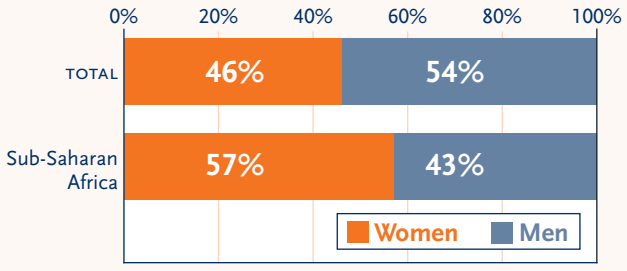
- **HIV vaccines:** The best long-term hope for HIV prevention is a vaccine, although developing an effective vaccine has proven to be a highly complex scientific challenge. Most experts predict that it could be 10 years or more before an HIV vaccine candidate is shown to be effective. An effective vaccine will likely need to stimulate two types of immune response, although most of the vaccine candidates developed to date are designed to target only one arm of the immune system. Currently, 30 HIV vaccine candidates are in clinical trials, including two in advanced efficacy or proof-of-concept trials.

WOMEN, HIV, AND NEW PREVENTION METHODS

Many of the new HIV prevention methods in development could be particularly beneficial for women, who account for roughly one-half of people living with HIV globally.[2] For many women, current prevention methods are inadequate—women often do not have the social or economic power to refuse sex or negotiate condom use.[3]

New tools such as cervical barriers, pre-exposure prophylaxis, and microbicides may provide women with HIV prevention methods that they could initiate—potentially without the knowledge or consent of their partners.

FIGURE 1. **People Living with HIV/AIDS, by Gender, 2005**



Source: UNAIDS, 2005

2. ACCELERATING HIV PREVENTION RESEARCH

As new HIV prevention approaches move forward into advanced stages of development, the world faces serious financial, logistical, and ethical challenges in completing ongoing prevention trials, and in mounting the additional large-scale trials that will be needed to fully test new prevention tools and strategies. Key challenges—and recommendations from the Global HIV Prevention Working Group—include:

- **Clinical trials capacity:** Current efficacy trials of new HIV prevention approaches will require a total of approximately 80,000 study participants. Even more participants will be needed to mount additional efficacy studies and to conduct confirmatory trials. Yet current global clinical trials capacity—including an adequate number of participants, properly equipped study sites, and trained research staff—falls far short of the need.

  Recommendations: *Trial sponsors, national governments, and international donors should make significant new investments in global capacity for HIV prevention trials. Agencies should work together to inventory existing capacity, determine specific needs in key regions, and identify sites for scaling up capacity. Given limited capacity, trial sponsors should better coordinate decision-making about which prevention interventions to prioritize for large-scale trials, and share trial sites as necessary.*

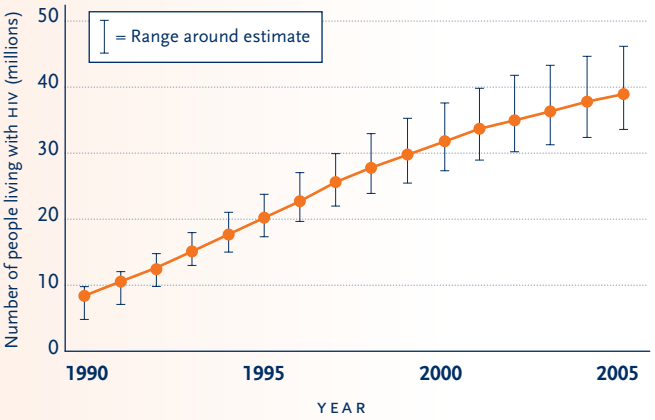
- **Ethical issues:** While current HIV prevention trials are being conducted according to internationally and locally accepted ethical standards, existing guidelines do not sufficiently address some key issues that have emerged in recent years. These include defining the standard set of existing prevention methods that should be provided to all trial participants; defining and ensuring fully informed consent; and determining how to facilitate HIV treatment access for participants who become HIV-infected during the course of a trial, or who are found to be HIV-infected at the initial screening for a trial.

  Recommendations: *Key stakeholders in HIV prevention research—including trial sponsors, affected communities, and developing country governments—should work with UNAIDS and the World Health Organization (WHO) to convene a broadly inclusive panel of experts to develop updated ethical guidelines for conducting HIV prevention research. This guidance should be continually revised as HIV prevention research evolves.*

- **Community engagement:** Community involvement and support are vital to successful clinical research. Yet some HIV prevention trials have been criticized for not properly reaching out to communities. In some cases, misinformation and lack of communication between researchers and communities have been factors in the cancellation of HIV prevention trials.

  Recommendations: *Investigators and sponsors of HIV prevention trials should foster strong partnerships with the communities where trials are conducted—through Community Advisory Boards, regular communications to the broader community, and involvement of key local and national officials. Community input should inform key aspects of the clinical research process, including development of trial protocols, recruitment of participants, and ongoing trial oversight. International agencies such as UNAIDS and WHO should compile and publish best practices in community engagement.*

FIGURE 2. **Global HIV/AIDS Epidemic, 1990–2005**



Source: UNAIDS, 2006

3. PREPARING FOR ACCESS

As soon as they are shown to be effective, new HIV prevention methods should be made accessible and affordable for people at risk. But the world is virtually unprepared to ensure rapid access. Key challenges and recommendations include:

- **Resources:** While there have been significant increases in global spending to fight the HIV/AIDS epidemic in recent years, there are still severe resource gaps. UNAIDS estimates that $11.4 billion will be needed annually for HIV prevention by 2008—two-and-a-half times current spending.[4] Ensuring timely, widespread access to new prevention methods will require significant additional resources. Many countries will need donor assistance to purchase new prevention tools such as pre-exposure prophylaxis, microbicides, and vaccines. New resources will also be needed to support provider training and community education programs, to ensure that new prevention methods are safely and properly implemented.

  Recommendations: *The international community—including major donors such as the Global Fund to Fight AIDS, Tuberculosis, and Malaria, and the U.S. government's President's Emergency Plan for AIDS Relief—should commit to providing the resources necessary to ensure the roll-out of new HIV prevention tools as soon as they are shown to be effective. It is critical to begin estimating now the resources that will be needed to implement new prevention methods. It is also vital that these resources do not take funding away from current HIV prevention, treatment, and care programs.*

- **Public health guidance:** As results become available from clinical trials, national and global decision-makers will need to carefully determine how to integrate new HIV prevention methods into health programs. In the case of new technologies such as microbicides and HIV vaccines, regulatory review and licensure will be required as well. Yet there are significant gaps in global capacity to provide timely public health guidance and regulatory review for new HIV prevention interventions.

  Recommendations: *Key stakeholders in HIV prevention—including national governments, donors, and international agencies such as UNAIDS and WHO—should establish systems to anticipate and provide needed guidance on the introduction of new prevention methods. Key issues include developing formal public health guidance on the proper use of new prevention approaches, and developing tools to help decision-makers in developing countries assess the relative cost and benefit of new prevention interventions. In addition, regulatory agencies in the U.S. and Europe should provide assistance to their counterparts in developing countries on evaluating new prevention methods.*

- **Provider training:** Health care professionals and community health providers will require training in the safe and proper use of new HIV prevention methods. For example, in many developing countries, few health care providers have experience in circumcising adult males, and if the procedure is improperly performed it can result in serious injury or death. The problem of health worker training is compounded by the fact that many developing countries suffer acute shortages of qualified health care personnel in general.

  Recommendations: *International agencies such as UNAIDS and WHO should develop regional and country-level provider training programs to help promote the safe and proper use of new HIV prevention methods. Where possible, training in providing new HIV prevention methods should be integrated into ongoing health provider training programs, and traditional healers should be included in these programs.*

- **Preventing "disinhibition":** It is essential that the introduction of new prevention methods does not lead people to become complacent about HIV risk behavior. Such behavioral disinhibition could cancel out the benefits of new HIV prevention methods, and lead to an inadvertent increase in HIV infections

  Recommendations: *Strong communications and public education campaigns, grounded in scientific evidence of effectiveness, should accompany the introduction of new prevention methods, to reinforce the importance of minimizing risk behavior and using new prevention methods in combination with existing tools and strategies. It is also critical to monitor and evaluate efforts to counter potential disinhibition on an ongoing basis to ensure they are effective.*

EXPANDING ACCESS TO EXISTING HIV PREVENTION APPROACHES

As research moves forward on new HIV prevention methods, it is also critical to expand access to existing prevention methods.

Fewer than one in five people at high risk for HIV currently have access to effective prevention (see figure 3).[5] According to an analysis by UNAIDS and the World Health Organization, expanded access to proven prevention strategies could avert half of the 62 million new HIV infections projected to occur between 2005 and 2015.[6]

The following tools and strategies are proven to reduce the risk of HIV transmission:[7]

Preventing Sexual Transmission

- **Behavior change, including abstinence and condom use:** A number of scientific studies have documented the effectiveness of behavior change programs that encourage people to adopt safer sexual behaviors. These include remaining sexually abstinent or delaying initiation of sexual activity, decreasing the number of sexual partners, and using condoms consistently and correctly if sexually active.
- **HIV testing:** Encouraging HIV testing is critical for prevention—people who know their HIV status are more likely to protect themselves and others from infection.
- **Diagnosis and Treatment of Other STDs:** Infection with other sexually transmitted diseases (STDs) such as gonorrhea increases the risk of HIV transmission, and prompt diagnosis and treatment of STDs can help reduce HIV risk.

Preventing Blood Borne Transmission

- **Harm reduction for injection drug users:** Harm reduction programs that provide clean needles and syringes have been proven to be effective in reducing the risk of HIV transmission among injection drug users, without contributing to an increase in drug use.
- **Blood supply safety:** Routine screening of the blood supply can virtually eliminate the risk of HIV transmission through donated blood.
- **Infection control in health care:** Countries that require health workers to adopt "universal precautions" such as wearing gloves and masks have succeeded in making HIV transmission extremely rare in health care settings.

Preventing Mother-to-Child Transmission

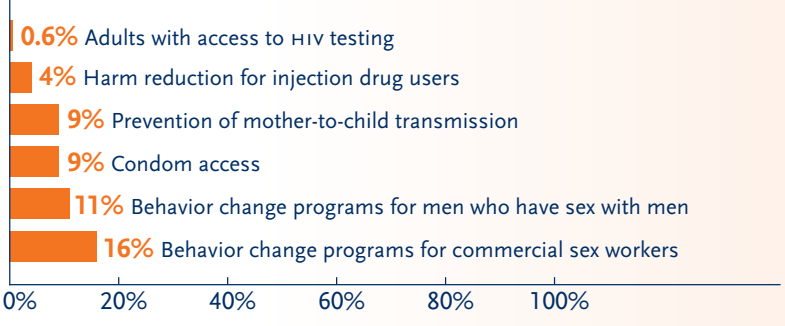
- **Antiretroviral drugs:** The inexpensive antiretroviral drug nevirapine can reduce the risk that an HIV-infected pregnant woman will transmit HIV to her child by nearly 50 percent. Combinations of antiretrovirals can reduce the risk even further.
- **Breastfeeding alternatives:** The chance of an HIV-infected mother transmitting HIV to her newborn increases by up to half with prolonged breastfeeding, and HIV-infected mothers should have access to breastfeeding alternatives.
- **Caesarean delivery:** Caesarean delivery significantly reduces the risk of mother-to-child HIV transmission.

Supportive Policies

HIV prevention is most effective when it is supported by strong and visible political leadership, and by policies that address the root causes of vulnerability to HIV, including:

- **Anti-stigma measures** that prevent discrimination against people with HIV and vulnerable groups
- **Gender-equality initiatives,** including programs to enhance women's education and economic independence, and laws to combat sexual violence and trafficking
- **Involvement of communities and HIV-infected individuals** in educating people about HIV, and in developing, implementing, and evaluating prevention programs
- **Visible political leadership** that prioritizes a comprehensive response to the HIV/AIDS epidemic, including prevention, treatment, and care

FIGURE 3. **Access to Existing HIV Prevention Methods**



Sources: UNAIDS, 2006; USAID et al., 2004

I. HIV PREVENTION RESEARCH: STATE OF THE SCIENCE

A range of promising new HIV prevention approaches are currently under investigation. If shown to be effective, these new tools and strategies could help avert millions of new infections, and have a substantial impact on the course of the HIV/AIDS epidemic. They include:

- Male circumcision
- Cervical barriers
- Pre-exposure prophylaxis with antiretrovirals
- Herpes suppression
- Microbicides
- HIV vaccines

Some of these new prevention methods—including male circumcision, cervical barriers, pre-exposure prophylaxis with antiretrovirals, and herpes suppression—could potentially be shown to be effective within the next few years. While the successful development of prevention methods such as microbicides and vaccines is likely to take longer, important progress is being made on these fronts as well.

Many of these new HIV prevention methods could be particularly beneficial for women, who represent approximately one-half of HIV infections globally, and nearly 60 percent of people living with HIV in sub-Saharan Africa.[8] Physiologically, women are more vulnerable to HIV infection than men. In addition, many women have difficultly negotiating abstinence and condom use with male partners, especially in countries where women lack legal rights and are economically dependent on men.[9]

It is important to note that there is no "magic bullet" for HIV, and that none of these new HIV prevention methods is likely to be 100 percent effective. All would require the continued use of current prevention methods that have already been proven to be effective—including behavior change programs, condoms, HIV testing, and treatment of other sexually transmitted diseases.[10] As discussed in section 3 of this report, it is also essential to ensure that risk behavior does not increase with the introduction of new prevention methods.

This section describes the state of research into new prevention tools and strategies. Figure 4 on page 7 summarizes current efficacy trials of new HIV prevention methods.

NEW HIV PREVENTION APPROACHES IN DEVELOPMENT

- **Male circumcision:** Observational studies have shown that countries with high rates of male circumcision—removal of the foreskin of the penis—have lower HIV infection rates.
- **Cervical barriers:** Cervical barriers, such as the diaphragm, cover the cervix, the site where most HIV infections in the female genital tract are believed to occur.
- **Pre-exposure prophylaxis with antiretrovirals:** Antiretroviral drugs, which improve the health of HIV-infected people, may also prevent HIV infection.
- **Herpes suppression:** Data suggest that infection with HSV-2, the primary cause of genital herpes, increases the risk of HIV acquisition and transmission. Suppressing herpes with the inexpensive, off-patent drug acyclovir may reduce HIV risk.
- **Microbicides:** Microbicides are topical substances applied to the vagina or rectum to potentially prevent HIV infection.
- **HIV vaccines:** Preventive vaccines enhance the body's immune defenses, enabling the immune system to fight off diseases that it cannot naturally control.

FIGURE 4.

CURRENT EFFICACY TRIALS OF NEW HIV PREVENTION METHODS

Prevention Method	Trial Sites and Participants	Primary Sponsors and Funders
Male Circumcision	Kenya—2,500 men	University of Illinois, U.S. National Institutes of Health (NIH)
	Uganda—5,000 men	Johns Hopkins University, NIH
	Uganda—1,361 men and 7,000 women	Columbia University, Gates Foundation
Cervical Barriers Female diaphragms	South Africa and Zimbabwe—5,045 women	University of California at San Francisco, Gates Foundation
Pre-Exposure Prophylaxis with Antiretrovirals		
Tenofovir	Thailand—1,600 injection drug users	U.S. Centers for Disease Control and Prevention (CDC)
Tenofovir plus emtricitabine	Botswana—1,200 men and women	CDC
	Peru—1,400 men who have sex with men	NIH
Herpes Suppression	Peru, South Africa, Zambia, Zimbabwe, and U.S.—3,277 men and women	University of Washington, NIH
	Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, and Zambia—3,000 male-female couples in which one partner is infected with HIV and HSV-2	University of Washington, Gates Foundation
Microbicides		
C31G (Savvy)	Nigeria—2,142 women	Family Health International (FHI), U.S. Agency for International Development (USAID)
Carbopol 974p (BufferGel)	Malawi, South Africa, Tanzania, Zambia, Zimbabwe, and U.S.—3,220 women	NIH
Cellulose sulfate	Nigeria—2,160 women	FHI, USAID
	Benin, Burkina Faso, India, South Africa, and Uganda—2,574 women	CONRAD, Gates Foundation, USAID
Naphthalene sulfonate (PRO2000)	Same as Carbopol trial (see above)	NIH
	South Africa, Tanzania, Uganda, Zambia, and Zimbabwe—10,000 women	U.K. Medical Research Council, U.K. Department for International Development
PC-515 (Carraguard)	South Africa—6,299 women	Population Council, Gates Foundation, USAID
HIV Vaccines		
gag, pol, nef in adenovirus type 5 (MrkAd5)	Australia, Brazil, Canada, Dominican Republic, Haiti, Jamaica, Peru, and U.S.—3,000 men and women	Merck & Co., NIH
env, gag, pol in canarypox + gp120 (ALVAC + AIDSVAX)	Thailand—16,000 men and women	Thailand Ministry of Public Health, NIH, U.S. Military HIV Research Program

MALE CIRCUMCISION

Male circumcision—removal of the foreskin of the penis—may reduce the risk of HIV acquisition and transmission during sexual intercourse.

Theoretical Basis

Observational studies have long noted that, on average, countries with high rates of male circumcision have lower HIV infection rates.[11] Circumcision may reduce HIV risk because the mucosal surface of the foreskin of the penis contains Langerhans cells that are highly susceptible to HIV infection.[12] Circumcision may reduce HIV risk directly, or have an indirect effect by preventing other sexually transmitted diseases that facilitate HIV acquisition and transmission.

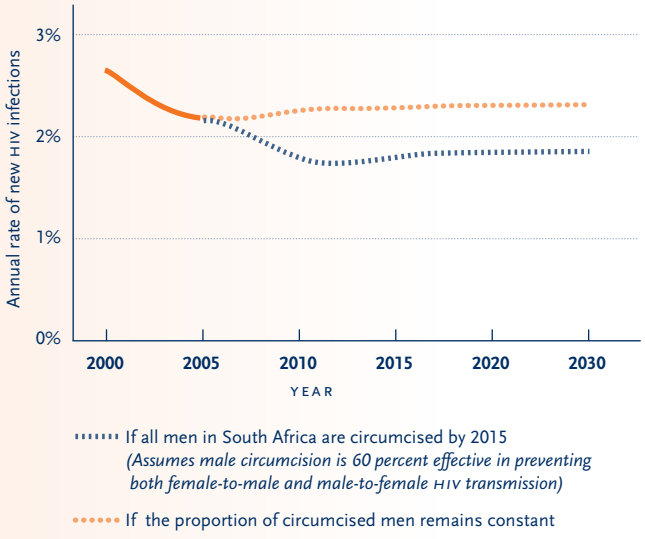
Status of Research

In 2005, French and South African researchers announced encouraging results from the first randomized clinical trial of the efficacy of male circumcision for HIV prevention. The investigators reported that men who were randomly assigned to receive circumcision had a 60 percent lower risk of subsequently acquiring HIV infection from female partners than men randomized to the control arm of the study, who were offered circumcision after the trial ended. The trial was conducted among 3,274 men in a community near Johannesburg, South Africa, and the findings have generated hope that circumcision could be an important new HIV prevention strategy.[13]

Three efficacy trials of male circumcision are underway in Kenya and Uganda, and UNAIDS and other international health agencies have emphasized the importance of waiting for these results before recommending widespread adoption of male circumcision for HIV prevention.[14] The trials in Kenya and Uganda involve more than 8,000 men, and are likely to offer important insights regarding the applicability of male circumcision in different settings. For example, the Uganda trials involve a broader age range (15–49) than the South Africa and Kenya trials (18–24), and use a different circumcision procedure (sleeve circumcision versus the forceps-guided procedure used in South Africa and Kenya). Results from these trials are expected in 2007.

In addition to studying the efficacy of male circumcision for preventing female-to-male HIV transmission, one of the trials in Uganda is following 7,000 women—including approximately 4,000 female partners of male participants in the circumcision trials—to determine if circumcising men also reduces the risk of HIV transmission from men to women, as suggested by observational data.[15]

FIGURE 5. **Potential Impact of Male Circumcision in South Africa**



Source: Williams et al., 2006

The findings among women in the Uganda trial could have important public health significance, because most HIV infections in women are the result of male-to-female transmission of the virus.

Potential Prevention Impact

Used in combination with other HIV prevention methods, male circumcision could have a substantial impact on reducing HIV acquisition and transmission. One modeling study predicts that widespread implementation of male circumcision could avert 2 million new HIV infections over the next 10 years in sub-Saharan Africa, and a further 3.7 million new infections over the 10 years after that (see figure 5 for South Africa projections).[16] Circumcision is also potentially important as a prevention option because it is a one-time intervention that could offer life-long benefit. Research indicates that circumcision would be acceptable to men in Africa: a study of adult males circumcised in Kenya found that 99 percent were satisfied with the procedure, as were their female partners.[17]

When performed by a trained practitioner, male circumcision is a safe procedure (typically defined as resulting in surgical complications in fewer than 2 percent of cases), and analgesia effectively mitigates pain. However, as noted in section 3 of this report, concerns have been raised about the safety of circumcision procedures performed by medical practitioners or traditional healers who have not been properly trained, underscoring the importance of coupling future introduction of male circumcision for HIV prevention with strong training and quality assurance initiatives.

CERVICAL BARRIERS

Cervical barriers such as the diaphragm and cervical caps are currently used with spermicides as contraceptives. Made of latex or silicone, they are inserted into the vagina to cover the cervix and serve as a barrier against sperm.

Theoretical Basis

Research suggests that most HIV infections in the female genital tract occur in the cervix and endocervix.[18] Cervical barriers such as diaphragms cover the cervix, and by doing so may significantly reduce women's risk of becoming infected with HIV. In addition, cervical barriers may prevent HIV by preventing infection with other sexually transmitted diseases that facilitate HIV transmission.

Diaphragm and lubricant gel

Status of Research

A clinical trial in South Africa and Zimbabwe is testing the efficacy of the latex diaphragm used with a non-contraceptive lubricant gel for preventing male-to-female HIV transmission. The trial involves 5,045 women and is comparing use of the diaphragm plus condoms with use of condoms alone. Results are expected in 2007.

Potential Prevention Impact

If proven to be effective for HIV prevention, cervical barriers such as diaphragms would have a number of distinct advantages. Diaphragms are inexpensive, reusable, and already approved and available for pregnancy prevention. In addition, diaphragms can be inserted in advance of sexual activity, left in place up to 24 hours, and potentially used without the knowledge of the woman's sexual partner. Studies in Zimbabwe suggest that the diaphragm is accepted among women at risk for HIV,[19] and women and their male partners prefer the diaphragm to other female-initiated prevention methods such as the female condom.[20]

Cervical barriers such as diaphragms could also potentially be used to deliver microbicides for HIV prevention (see discussion of microbicides on page 12).

PRE-EXPOSURE PROPHYLAXIS WITH ANTIRETROVIRALS

Antiretroviral drugs, which improve the health of HIV-infected people, may also prevent HIV infection.

Theoretical Basis

Antiretroviral drugs, which have improved the health and prolonged the lives of people infected with HIV, are currently also used to prevent some forms of HIV transmission. Timely administration of antiretrovirals reduces the risk of HIV transmission from HIV-infected mothers to their newborns,[21] and to health care workers with occupational percutaneous exposure to HIV (i.e., by needle stick), if administered shortly after exposure.[22] It is hypothesized that daily pre-exposure administration of antiretrovirals to HIV-uninfected individuals may prevent HIV infection by disabling or interfering with HIV within the initial period after an individual is exposed to it.

Status of Research

In recent years, researchers have begun studying the antiretroviral drug tenofovir, taken as a once-daily pill, as a potential new method to prevent HIV infection in high-risk individuals, an approach known as pre-exposure prophylaxis, or PREP. Tenofovir is approved for the treatment of HIV infection; it is especially long-lasting in the body, unusually slow to cause HIV to develop resistance, and rarely causes serious side effects.[23] In monkey studies, tenofovir has shown promise in preventing infection with HIV-like viruses,[24] although other animal studies have suggested that tenofovir's effectiveness may decrease over time.[25]

Researchers are also beginning to test a combination pill containing tenofovir plus emtricitabine.[26] A monkey study with the combination regimen showed that it provided strong protection against HIV-like infection.[27]

Over the past few years, a number of clinical trials have been initiated to evaluate the safety and efficacy of pre-exposure prophylaxis with antiretrovirals for HIV prevention:

- *Safety:* Data on the safety of administering tenofovir to HIV-uninfected people has been collected from trials involving more than 900 women in Ghana, Cameroon, and Nigeria. An additional safety trial is ongoing among men in the United States.
- *Efficacy:* Clinical trials to assess the efficacy of daily administration of tenofovir, or tenofovir plus emtricitabine,

for HIV prevention are being conducted in three countries—Botswana, Peru and Thailand. The trials will enroll approximately 4,200 participants from a number of groups at high risk for HIV, including injection drug users, men who have sex with men, and high-risk women. The first results on the efficacy of pre-exposure prophylaxis for HIV prevention could be available by 2007 or 2008.

Research is in earlier stages for the potential prevention application of other antiretroviral agents, including new classes of drugs that are also being developed as potential HIV treatments.

Potential Prevention Impact

If shown to be effective, pre-exposure prophylaxis with antiretrovirals could be an important new prevention method for people at high risk for HIV infection. A modeling study sponsored by AIDS Partnership California concluded that providing PREP to high-risk groups such as men who have sex with men, injection drug users, and high-risk women could quickly reduce the rate of new HIV infections, depending on the level of PREP's efficacy, and the percentage of people at risk who received the intervention.[28]

While PREP is likely to be more expensive than other new HIV prevention methods under investigation, if found to be highly efficacious, studies suggest it could nonetheless be a cost-effective prevention method for high-risk groups, when used in combination with other prevention methods.[29]

One potential concern regarding pre-exposure prophylaxis is resistance. Any resistance developed to antiretrovirals such as tenofovir when used for prevention could limit the usefulness of the drugs for later HIV treatment. Several of the ongoing or planned trials are examining this important question.

RESEARCH TO IMPROVE EXISTING PREVENTION METHODS

In addition to efforts to develop new HIV prevention methods, researchers are exploring ways to improve the prevention impact of existing approaches:

- **Next-generation female condoms:** The FC® female condom was developed in the 1990s by the Female Health Company and provides an alternative to male condoms for the prevention HIV and other sexually transmitted diseases.[33] However, the product, which is made of polyurethane, has not been widely used because of its relatively high cost. The Female Health Company is developing a new female condom made of synthetic latex (nitrile polymer), which is expected to be considerably less expensive. Other organizations, including the Program for Appropriate Technology in Health, are also working on other models of female condoms. The World Health Organization (WHO) is currently reviewing data on the new female condom to determine its suitability for use in HIV prevention. The redesign of the female condom could also facilitate its use for HIV prevention during anal sex, for both heterosexual couples and men who have sex with men.[34]

- **Treatment of drug addiction:** Methadone is currently used to treat addiction to opiate drugs such as heroin, and has been shown to reduce the risk of HIV transmission through injection drug use. Although roughly three-quarters of people who initiate methadone maintenance therapy respond well, the intervention does not suit all patients with opioid dependence.[35] Researchers are testing buprenorphine in China and Thailand as an alternative to methadone for treating heroin addiction and reducing HIV risk. The U.S. Food and Drug Administration has already approved buprenorphine for treatment of heroin addiction when administered by a physician, and buprenorphine is also prescribed in several European countries. WHO has added both methadone and buprenorphine to its List of Essential Medicines.

- **Improved mother-to-child prevention strategies:** Researchers are studying ways to improve the effectiveness of current strategies for preventing mother-to-child transmission. For example, a clinical trial in Africa will assess an extended regimen of the antiretroviral drug nevirapine to reduce the risk of HIV transmission to newborns during breastfeeding. Other clinical trials will test a range of antiretrovirals for mother-to-child prevention. At the same time, an important shortcoming of mother-to-child prevention programs is the fact that they reach fewer than 10 percent of women who could potentially benefit from them.[36] WHO has identified research into the barriers to providing access to existing mother-to-child prevention programs as a top priority.

- **Improved behavior change strategies:** Researchers are studying ways to strengthen behavior change

HERPES SUPPRESSION

Data suggest that infection with herpes simplex virus type 2 (HSV-2), the primary cause of genital herpes, increases the risk of HIV acquisition and transmission. Suppressing HSV-2 with the inexpensive, off-patent drug acyclovir may reduce HIV risk.

Theoretical Basis

An HIV-uninfected individual is up to three times more likely to contract HIV infection during sexual intercourse if he or she is infected with HSV-2.[30] In addition, because HSV-2 appears to accelerate HIV replication and shedding, HIV-infected individuals may be more likely to transmit HIV if they are also infected with HSV-2.[31]

Researchers aim to determine whether the drug acyclovir, which suppresses HSV-2, can help reduce the risk of HIV transmission.* Acyclovir is safe and well tolerated, and slow to cause HSV-2 to develop resistance in both HIV-infected and HIV-uninfected people.[32]

Status of Research

Two clinical trials are evaluating the efficacy of suppressing HSV-2 with acyclovir as an HIV prevention strategy. The first trial involves 3,227 men and women who are infected with HSV-2 but uninfected with HIV in

* *It is important to note that even if herpes suppression is not proved efficacious for HIV prevention, expanded access to acyclovir treatment could significantly decrease the global burden of herpes.*

interventions that encourage people at high risk for HIV infection to reduce risk behavior. For example, a clinical trial in Thailand and the United States will test a peer-based HIV prevention program for injection drug users. In the trial, injection drug users will be given a four-week training course to learn skills for educating other drug users about ways to reduce the risk of HIV acquisition and transmission.

- **New "prevention for positives" strategies:** Because so few people in developing countries are aware of their HIV status,[37] prevention programs have often relied on general messages that implicitly assume that all individuals are HIV-uninfected—an approach that may be limiting the effectiveness of HIV prevention efforts. Although a positive HIV test result typically prompts HIV-infected people to avoid transmitting HIV to others,[38] evidence in developed countries indicates that a notable share of people with HIV infection have difficulty implementing and sustaining safer behavior.[39] In recent years, WHO, the International Planned Parenthood Federation, and the U.S. Centers for Disease Control and Prevention, among others, have begun examining behavior change strategies tailored specifically for people living with HIV.[40]

- **Antiretroviral therapy to reduce the risk of HIV transmission:** Antiretroviral therapy reduces viral load in HIV-infected individuals, and studies have shown that lower viral load is strongly associated with lower transmission risk.[41] On this basis, it has been hypothesized that appropriate therapeutic administration of antiretrovirals may reduce the infectiousness of people with HIV and their likelihood of transmitting the virus to others. Currently, 1,700 HIV-discordant couples are being enrolled in a six-country, seven-year clinical trial to assess whether administering combinations of antiretrovirals to HIV-infected individuals reduces the risk of HIV transmission. The trial is also assessing whether the prevention impact of antiretroviral therapy can be enhanced by administering antiretrovirals to HIV-infected people earlier than would currently be medically indicated.

- **Improving the safety of health care injections:** Unsafe injections and blood-draws in health care settings account for an estimated 5 percent of new infections worldwide.[42] In 1999, WHO, UNICEF, and the United Nations Population Fund issued a joint statement identifying the inexpensive "auto-disable" syringe as the "equipment of choice" for routine and mass immunization.[43] However, as of 2004, 38 percent of developing countries did not use auto-disable syringes in their immunization programs.[44] In addition to ensuring universal adoption of auto-disable syringes, research efforts in both public and private sectors continue to focus on other methods to improve injection safety.

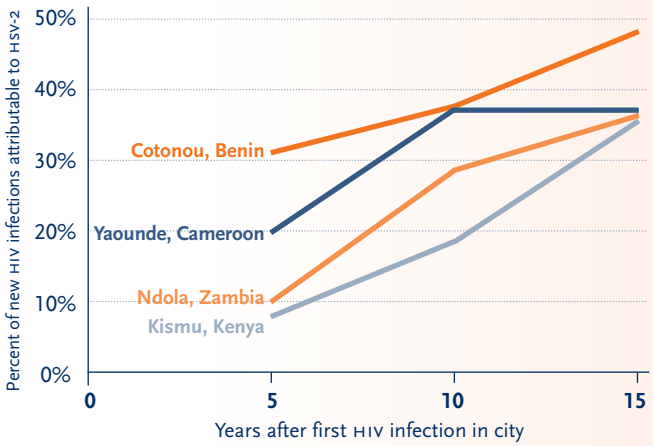
Africa, Latin America, and the United States; this study will help determine whether HSV-2 suppression decreases the risk of HIV acquisition. The second trial involves 3,000 HIV-discordant couples in Africa in which one partner is infected with both HIV and HSV-2 and the other is not HIV-infected. This study will help determine whether HSV-2 suppression decreases the likelihood that people infected with HIV will transmit it to others. Results are expected in 2007 for the trial among HIV-uninfected people, and in 2008 for the trial among HIV-discordant couples.

Potential Prevention Impact

If proven to be effective and used in combination with other prevention methods, suppression of HSV-2 with acyclovir could significantly strengthen efforts to reduce sexual HIV transmission. In some parts of southern Africa, up to 70 percent of adults are infected with HSV-2,[45] and a recent four-city study in Africa linked HSV-2 with more than one-third of all new HIV infections over a 15-year period (see figure 6).[46]

From a cost perspective, acyclovir is an attractive prevention option. Because its patent has expired, the drug is inexpensive and already available in many developing countries.

FIGURE 6. **Four-City Study: Herpes Infection Fuels HIV Spread**



Source: Freeman et al., 2005

MICROBICIDES

Microbicides are topical substances designed to be applied to the vagina or rectum to prevent HIV infection. Some vaginal microbicides may also prevent pregnancy.

Theoretical Basis

Microbicide candidates currently in research and development are designed to operate in a variety of ways to prevent HIV infection. These include:

- Disabling HIV
- Providing a barrier between HIV in semen and vaginal or rectal tissue
- Interfering with the process by which HIV enters cells and establishes infection
- Strengthening the body's natural defenses against HIV[47]

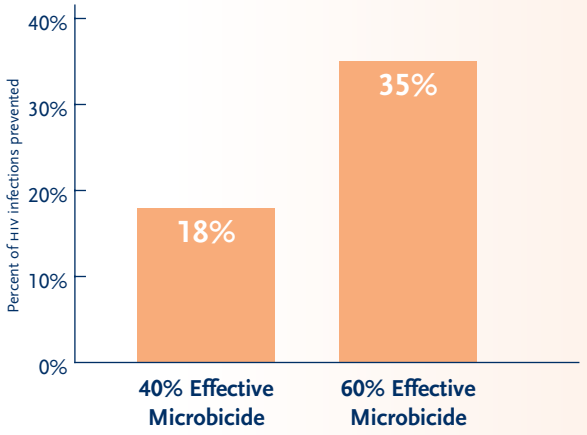
Status of Research

As of mid-2006, the microbicide research pipeline included 28 candidate products.[48] Microbicide candidates can be divided into two groups, first- and second-generation candidates.

First-generation microbicide candidates: Five microbicide candidates—all formulated as clear, colorless gels—are furthest along in development and are being tested in large-scale clinical trials for efficacy:

- *C31G (Savvy)* is a surfactant compound designed to disable HIV by breaking down its outer membrane. The product is being tested in a clinical trial involving 2,142 women in Nigeria. C31G may also protect against pregnancy.
- *Carbopol 974p (BufferGel)* is a buffering compound designed to function as a barrier between HIV in semen and vaginal tissue. It is also designed to maintain the vagina's acidity in the presence of semen, which may help kill or disable HIV. Carbopol is being tested in a clinical trial involving 3,220 women in five African countries and the United States. Carbopol may also prevent pregnancy.
- *Cellulose sulfate* is an attachment inhibitor that aims to prevent HIV from attaching to cells in the vaginal wall. A 2,160-participant trial has begun in Nigeria, and a second trial among 2,574 women has started in four African countries and India. Cellulose sulfate may also prevent pregnancy.
- *Naphthalene sulfonate (PRO2000)* is similar to cellulose sulfate, and is designed to prevent infection by binding to HIV and interfering with its ability to attach to and

FIGURE 7. **Potential Impact of a Partially Effective Microbicide Over Four Years in Northern Karnataka, India**



Source: International Family Health, 2004

enter cells. The candidate is being tested in the same 3,220-participant trial as Carbopol (see above), and a separate trial is underway among approximately 10,000 participants in five African countries.

- *PC-515 (Carraguard)* is also an HIV attachment inhibitor. Its active ingredient, carrageenan, is derived from seaweed. A clinical trial is underway in South Africa involving 6,299 women.

The first results from efficacy trials of first-generation microbicide candidates could potentially be available in 2008.

Second-generation microbicide candidates: While the microbicide candidates above are in late-stage trials and could potentially be shown to be effective within the next five years, there is growing interest in second-generation microbicide approaches that are approximately 10 years away from completing testing. Second-generation microbicide candidates specifically target HIV or molecules of the cells it infects, and some of these microbicide approaches involve using existing or new classes of antiretroviral compounds as microbicides.[49]

Researchers are also investigating new ways of formulating microbicides, such as using them in vaginal rings or cervical barriers.[50] In addition, although most development efforts have concentrated on vaginal microbicides, a number of early research projects are advancing the development of rectal microbicides, which could reduce the risk of HIV transmission during anal sex.[51]

Potential Prevention Impact

A modeling study from the London School of Hygiene and Tropical Medicine estimated that a 60 percent effective microbicide could avert 2.5 million new HIV infections in low- and middle-income countries over three years.[52] A separate modeling project concluded that a microbicide that is 60 percent effective against HIV and other STDs could prevent more than one-third of new HIV infections that are projected to occur over four years in a district in northern Karnataka, India, where infection is migrating from high-risk groups to the broader population (see figure 7).[53]

Other studies have predicted that even a microbicide with a relatively low effectiveness rate could prevent 9 percent of new infections over four years in a high-prevalence neighborhood of Johannesburg, South Africa, and nearly 40 percent of new infections projected in a lower-prevalence setting in Benin.[54]

Like many of the other new HIV prevention methods in development, microbicides would be female-initiated, and may be able to be used by women without requiring the cooperation of male partners. Developers of potential microbicides have conducted extensive research into the acceptability of their products, and evidence to date indicates that women and men in both developing and developed countries are interested in using microbicides. Further research is needed to identify the specific product characteristics that would be most acceptable to women and men.[55]

HIV VACCINES

Preventive vaccines enhance the body's immune defenses, enabling the immune system to fight off diseases that it cannot naturally control.

Theoretical Basis

The ultimate goal for an HIV vaccine is to prevent HIV infection. Scientists have identified rare individuals whose immune systems appear to have a natural ability to resist HIV infection, a finding that provides clues for the design of an effective vaccine.

However, an HIV vaccine that does not prevent infection but, in the event of infection, suppresses the amount of virus circulating in the body could also have a substantial impact. Such a vaccine would work much like antiretroviral drugs that lower viral load in order to keep people with HIV healthy, except that a vaccine would stimulate the immune system to do this, rather than

requiring daily doses of medicine. An HIV vaccine that lowered viral load may also reduce HIV transmission.

Status of Research

Developing an effective HIV vaccine has proven to be a highly complex scientific challenge, and most research is at an early stage.[56] To date, traditional vaccine designs have not worked for HIV, in part because the virus is able to evade the immune system by rapidly mutating. Some experimental vaccines have been shown to protect monkeys from HIV-like viruses, although the results have not yet been replicated in humans.[57]

The one HIV vaccine candidate to complete the full course of clinical trials was found to be ineffective.[58] More than 30 other HIV vaccine candidates are currently in clinical trials, including two vaccine candidates in advanced efficacy or proof-of-concept trials (see figure 4 on page 7).[59]

Most experts predict that it will be 10 years or more before an HIV vaccine is shown to be effective. A major challenge facing researchers is that it is likely that an effective vaccine will need to stimulate the immune system's two main arms, called humoral immunity (broadly neutralizing antibodies) and cellular immunity. Most HIV vaccine candidates currently being tested are designed only to stimulate cellular immunity, and research is in the very early stages

FUNDING FOR HIV PREVENTION RESEARCH

Only a small percentage of total global spending on biomedical research and development focuses on HIV/AIDS and other diseases that primarily affect developing countries.[63] Funding for research on new HIV prevention methods is inadequate.

The best available information on funding for HIV prevention research is for microbicide and vaccine development (see figure 8):[64]

- **Microbicide funding:** The HIV Vaccines and Microbicides Resource Tracking Group estimates that a total of $142 million was invested worldwide in microbicide development in 2004. The public sector was the main source of this funding, accounting for 87 percent of total funding. The United States provided nearly three-quarters of public sector funding—largely through the National Institutes of Health and the U.S. Agency for International Development. European governments and the European Commission provided roughly one-quarter of public sector funding in 2004.
- **HIV vaccine funding:** In 2004, an estimated total of $682 million was spent on HIV vaccine development, of which 88 percent was public sector funding. U.S. government agencies provided a significant share (86 percent) of this funding.

Although current levels of funding for microbicide and vaccine development represent substantial increases over previous years—public sector investments in both microbicide and HIV vaccine development doubled between 2000 and 2004—far more resources are needed. The International Partnership for Microbicides (IPM) has called for an additional $280 million to be invested in microbicide development annually, and the Global HIV Vaccine Enterprise has urged an additional $500 million annually to fully fund HIV vaccine development.[65]

Experience thus far underscores the critical need for increased financing for prevention research. In some cases, large-scale efficacy trials for new prevention approaches have proven to be significantly more expensive than originally anticipated. As this report describes in section 2, large prevention trials require substantial outlays for pre-trial epidemiological and behavioral studies, involve time-consuming efforts to enroll sufficient participants, and require close monitoring by well-trained clinical and non-clinical staff. The emergence of effective new prevention methods that may need to be included as part of the standard package of prevention interventions offered to all trial participants could further increase the cost of future prevention trials by requiring the enrollment of significantly larger numbers of trial participants.

Increasing Private Sector Investments

Private industry has generally been reluctant to invest in new health products intended for primary use in developing countries because of the concern that these products are unlikely to obtain a return on investment. While public and philanthropic financing has a played a vital role in advancing research on new prevention methods, it cannot replace the unique contributions of the private sector. Expertise regarding development and licensure of new health products resides largely with the private sector—failing to capitalize on the essential know-how of private industry will inevitably slow efforts to develop new methods to prevent HIV transmission.[66]

to identify vaccine candidates capable of stimulating broadly neutralizing antibodies.[60]

Recently, a number of leading HIV vaccine research agencies and funders formed a cooperative alliance to accelerate progress in developing an HIV vaccine. The Global HIV Vaccine Enterprise seeks to overcome the major scientific challenges to developing an HIV vaccine by bringing new collaboration, strategic focus, and resources to the field.[61]

Potential Prevention Impact

A preventive vaccine is the best long-term hope to control the global HIV epidemic. Vaccines have been successfully developed for other serious viral diseases—including polio and hepatitis B—and have been critical to controlling these diseases.

For HIV, a number of modeling studies suggest that even a partially effective vaccine could have a substantial impact on the course of the epidemic, although—like other prevention approaches—it would need to used in combination with other proven methods. For example, a modeling study by the World Bank found that a 50 percent efficacious HIV vaccine could reduce HIV infection rates by up to 60 percent in developing countries, provided that it was delivered to a majority of adults at risk.[62]

FIGURE 8. **Spending on Microbicide and HIV Vaccine Development, 2000 – 2004**

	2000	2001	2002	2003	2004
Microbicides					
Public sector	36	62	81	90	124
Philanthropic sector	29	3	25	17	18
Total microbicides	**65**	**65**	**106**	**107**	**142**
HIV Vaccines					
Public sector	307	359	436	532	602
Philanthropic sector	20	7	112	15	12
Private sector*					68
Total HIV vaccines	**327**	**366**	**548**	**547**	**682**

US$ MILLIONS

* Private sector spending figures available only for HIV vaccines in 2004

Source: HIV Vaccines and Microbicides Resource Tracking Group, 2005

A number of public policy measures have been proposed to encourage greater private sector engagement in research and development for HIV/AIDS and other diseases that primarily affect developing countries. These include:

- **Direct financing:** The public and philanthropic sectors can provide direct financing to private companies to conduct research. In exchange, the companies agree to make any resulting products available at affordable prices in low-income countries. This approach is being pursued by a number of public-private partnerships, such as IPM and the International AIDS Vaccine Initiative.
- **Patent extensions:** The Project Bioshield II legislation introduced in 2005 in the U.S. Congress proposed that companies that successfully develop new HIV prevention tools could extend the patent on any other product in their portfolio.
- **Predictable markets:** Governments and donors could make legally binding agreements to pay a specific price for a specific quantity of a product, should it be successfully developed.[67] For example, the G-8 is exploring "advance purchase commitments" to help spur companies to develop new tools to fight major global health problems such as malaria.

These approaches are designed to generate greater private sector investment in biomedical research by reducing uncertainties in the market for new health technologies in developing countries. Other non-financial reforms—such as improved demand forecasting, strong expressions of political commitment by developing country leaders to put new technologies to use, and measures to strengthen health service delivery systems—are discussed in section 3 of this report.

2. ACCELERATING HIV PREVENTION RESEARCH

The proper design and conduct of clinical trials is essential to the development of any new health tool or strategy.[68]

Clinical trials can be complicated and expensive. This is especially true for HIV prevention trials, which often require thousands of trial participants, who must be followed for up to several years in order to reliably detect whether the prevention method being studied is effective in reducing HIV transmission. Because it is critical to test new health tools and strategies under the conditions in which they will ultimately be used, many HIV prevention trials are conducted in developing countries where the need is most acute. This can increase their complexity, since clinical trials infrastructure in many developing countries often needs to be established in order to conduct a trial.

As a result of the expanding pipeline of new prevention methods and the increasing complexity of trials, substantial additional clinical trials capacity will be needed to prevent delays in testing new prevention methods. New ways of doing business are also needed to prioritize testing of the prevention methods that offer the greatest public health promise, and to promote collaboration among researchers to ensure the optimal use of scarce trial resources.

This section examines the following issues related to accelerating the pace of HIV prevention research, and ensuring that HIV prevention trials are conducted properly:

- Creating substantial additional clinical trials capacity that can be readily adapted for testing a range of new prevention methods, and identifying populations to participate in trials
- Resolving critical issues pertaining to the ethical conduct of HIV prevention trials
- Engaging affected communities as key partners in prevention research

ACCELERATING HIV PREVENTION RESEARCH—KEY RECOMMENDATIONS

- **Clinical trials capacity:** To avoid delays in testing promising new HIV prevention methods, leading trial sponsors, governments, and international donors should make significant new investments in increasing global capacity for HIV prevention trials. There is also a need to strengthen regulatory capacity to review trial protocols.
- **Trial design:** Researchers should develop improved models for accurately estimating the number of participants needed for HIV prevention trials, and create innovative trial designs that could reduce the number of participants needed to obtain valid results.
- **Coordination among trial sponsors:** Trial sponsors and international agencies should develop clear criteria to prioritize prevention methods for clinical trials. Sponsors should share data and information, and ensure that study sites can be adapted as needed and appropriate to test different prevention interventions.
- **Ethical issues:** Trial sponsors and international agencies should convene a broadly inclusive panel of experts to develop formal guidance on ethical issues in HIV prevention research that have recently emerged and are not addressed by existing guidance.
- **Community engagement:** Investigators and sponsors of HIV prevention trials should ensure meaningful involvement of local communities in trial design and conduct.

CLINICAL TRIALS CAPACITY

Global capacity to conduct HIV prevention clinical trials falls far short of what will be needed to expedite the development and testing of promising new prevention approaches over the coming years. Unless immediate steps are taken to increase the number of sites prepared to conduct HIV prevention trials, the world could soon face a situation where there is a pipeline of promising new prevention methods ready for trials, but inadequate capacity to test them.

Developing Additional Clinical Trial Sites

As research on new HIV prevention methods advances, the need for additional sites to conduct clinical trials will increase sharply. For example, in addition to the five microbicide candidates currently in large-scale clinical trials, a number of other candidates are in earlier stages of trials, and still more candidates are undergoing pre-clinical investigation. Key issues include:

- **Recruitment and retention of potential participants:** Fully testing just one new HIV prevention method for safety and effectiveness typically requires thousands of trial participants. Current efficacy trials of new HIV prevention approaches will require a total of approximately 80,000 participants, with most of this capacity needed in developing countries.
- **Confirmatory and bridging trials:** Although a number of large-scale trials of new HIV prevention methods are underway, and some are already fully enrolled, these trials are unlikely to be the definitive word on the effectiveness of these tools and strategies. New health interventions typically must be tested in multiple large-scale trials, to confirm the results and ensure they are accurate and broadly applicable.[69] For example, in a review of 39 heavily cited randomized clinical trials, nine of the trials were contradicted by subsequent trials, underscoring the importance of confirming early results.[70] In addition, for entirely new technologies such as microbicides and HIV vaccines, it is probable that the first candidate products to be found efficacious will have shortcomings, and it is likely there will need to be an iterative process of refinement and improvement, which will require substantial trials capacity. Furthermore, "bridging" trials are sometimes needed to determine the applicability of new health interventions in settings or populations that differ markedly from those in which the original trial was conducted.
- **Infrastructure and training:** To develop new trial sites in developing countries, trial sponsors, national governments, and donors must invest substantial additional resources in building physical infrastructure and training staff. In a multi-center trial, for example, the failure of a single trial site to adhere to international standards for good clinical practice may undermine the ability to draw definitive conclusions from the trial.
- **Basic health services:** Preparing a trial site also requires ensuring that there is sufficient capacity to provide basic health services in the community to support the trial, such as HIV testing and counseling, access to condoms and other supplies, and referrals to medical care when needed. These resources are vital to the successful conduct of any prevention trial, yet they are lacking in many developing countries.
- **Regulatory capacity:** Regulatory authorities play an important role in the approval and oversight of clinical trials. Greater regulatory capacity, particularly in developing countries, is needed to ensure that HIV prevention trial protocols are thoroughly and efficiently reviewed before the trials begin. (See section 3 of this report for a full discussion of regulatory capacity issues.)

Recommendations

- **New investments in trials capacity:** Leading sponsors of HIV prevention research, national governments, and international donors should make significant new investments in increasing global capacity for HIV prevention trials. Agencies should inventory existing capacity, identify specific needs in key regions, and prioritize sites for scaling up capacity. Increased resources should also be directed toward increasing regulatory capacity, particularly in developing countries, to help expedite review and approval of prevention trials. It is important, however, that scarce resources are not diverted from other health care needs, since many countries already face acute shortages of doctors and nurses.
- **Collaboration on HIV prevention research:** Leading sponsors of HIV prevention research—including bilateral donors, public sector biomedical research agencies, and leading foundations—should undertake joint planning and information-sharing to expedite developing new clinical trial sites for HIV prevention research. It is also critical for sponsors of prevention trials to collaborate with sponsors of HIV treatment studies, to identify opportunities for clinical trials

capacity to be shared and used to optimal benefit across prevention and treatment research.

- **Confirmatory trials:** To ensure as little delay as possible in bringing new prevention tools to people in need, leading sponsors of HIV prevention research should plan—at the outset of a clinical trial—for confirmatory or bridging trials that may be needed after the original trial is completed.

Cohort Development

Clinical trials determine if a new HIV prevention method is effective by comparing the rate of new HIV infections among individuals who receive the intervention with the rate of new infections among a control group of individuals who do not receive the intervention. In order to yield valid results, the population being studied must be similar to the population that would benefit most from the intervention under study.[71]

As part of the process of mounting a major prevention trial, researchers undertake epidemiological studies to identify populations with appropriate behavioral and demographic characteristics to be enrolled in the trial—so-called "cohorts"—including those with high rates of HIV infection. However, in some cohorts currently enrolled in prevention trials, there have been much lower rates of infection during the trials than researchers had expected based on pre-trial estimates. For example, in one site studying pre-exposure use of tenofovir, HIV incidence was found to be one-third as high as pre-trial studies estimated it would be.[72] This difference could stem from a variety of factors, including the positive impact of the other prevention services that are routinely provided to trial participants. Nonetheless, such a difference is critical, since it may require enrolling significantly more participants to yield statistically significant results.

Key issues in identifying appropriate cohorts for HIV prevention trials include:

- **Accurately estimating HIV incidence:** An accurate estimate of HIV incidence—that is, the rate of new HIV infections in the study population—is needed to enable researchers to project with accuracy the number of participants that will be needed for a given trial. While obtaining information on HIV prevalence—the proportion of people currently infected in a particular population—can be relatively straightforward, it is much more difficult to obtain a valid estimate of incidence, and to discern the characteristics of those who are more likely than others to become infected. In addition, the likely impact of other prevention services provided to trial participants must be taken into account when estimating needed trial size.

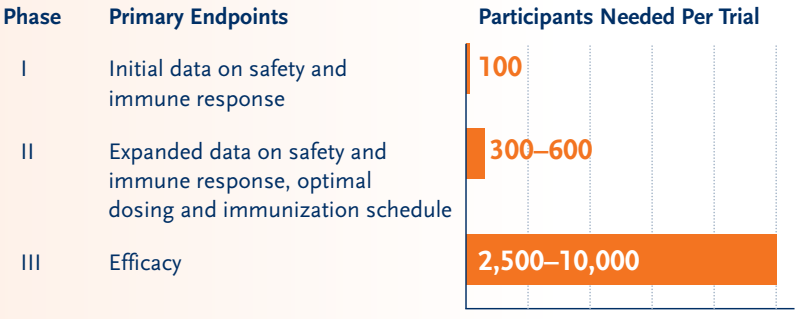
- **Challenges in enrolling and retaining participants:** In some trials, enrollment of trial participants has taken significantly longer than anticipated, and drop-out rates can be high. In some prevention trials that have enrolled large numbers of women of childbearing age, substantial numbers of participants have become pregnant and were required—temporarily or permanently—to drop out of the study. A large number of drop-outs can compromise the ability of a trial to arrive at valid conclusions.

Recommendations

- **Enhancing models for estimating trial size:** Principal investigators from past and ongoing prevention trials should collaborate with leading sponsors of prevention research, the World Health Organization (WHO), the U.S. Centers for Disease Control and Prevention (CDC), and other agencies to develop improved models for accurately estimating HIV incidence in trial populations and the number of participants that should be enrolled. Researchers should take into account the likelihood of participant drop-outs due to pregnancy and other factors. Until improved models are developed to estimate needed trial size, investigators should overestimate the number of participants needed, in order to increase the likelihood that the trial will have sufficient statistical power.

- **New trial designs:** Researchers should develop new trial designs that shorten the time and participants

FIGURE 9. **Phases of HIV Vaccine Clinical Trials**



Source: Klausner et al., 2003

required to identify effective interventions, as well as develop new methods of increasing retention of trial participants. In addition, to minimize the number of pregnant women who must discontinue or suspend participation in HIV prevention trials, more research is needed to assess the safety of new prevention methods during pregnancy, and to identify ways that pregnant women may be able to be safely retained in trials.

Prioritizing Among Multiple Candidates

At present, clinical trials capacity is typically developed by individual trial sponsors or investigators in order to test a specific product that they are researching, without considering how that capacity might be used by other sponsors or investigators. As a result, limited trials capacity may not be used strategically to test the most promising products first. In addition, trials may miss opportunities to undertake complementary behavioral studies or other research that might advance knowledge in the field as a whole.

In some cases, a better-financed sponsor may advance its own product through clinical trials even when other sponsors' products appear more promising. In other cases, a product may be pushed forward simply because it is the first to be available for testing, even though more promising candidates are in earlier stages of development. This approach can waste resources, as well as erode general confidence in the field if disappointing trial results are reported. For example, in the case of microbicide and HIV vaccine development, while the mounting of large-scale trials should be viewed as significant progress for the field, questions have also been raised regarding whether the microbicide and vaccine candidates that have proceeded to advanced trials are sufficiently different from each other to warrant testing each among large numbers of participants.

Recommendations

- **Prioritizing prevention candidates:** Key stakeholders should develop clear criteria and mechanisms for prioritizing among multiple prevention methods for large-scale clinical trials. For example, researchers could agree to use comparable tests for assessing potential new HIV prevention methods, openly share information, and agree to common benchmarks at each stage of the research process for determining whether a new prevention method is sufficiently promising to warrant further development. Some efforts are already underway to increase coordination among

FIGURE 10. SITES OF CURRENT HIV PREVENTION EFFICACY TRIALS

trial sponsors—including a working group of donors that support microbicide clinical trials, and the Global HIV Vaccine Enterprise—and these efforts should be strengthened and expanded.[73]

- **Flexible trial sites:** Where feasible, trial sites should be capable of being adapted for testing a range of different new prevention methods, including those developed by different sponsors and investigators, and prevention trial sites should be shared with HIV treatment research programs as appropriate. In awarding grants for prevention research, the major funders of such research should make such funding contingent on researchers' agreement to create flexible research sites that may be used for the most appropriate and promising research, regardless of sponsor.

ETHICAL CONDUCT OF PREVENTION TRIALS

All clinical trials must adhere to ethical standards that are recognized both internationally and in the local community in which the trial occurs.[74] While the HIV prevention trials that have been conducted to date have adhered to these standards, new issues have arisen that are not addressed by existing ethical guidance, and that must be resolved in order to ensure the proper design and rapid conduct of trials. In particular, clarity is needed on the following issues:

- Provision of appropriate prevention counseling and interventions to trial participants
- Provision of antiretroviral treatment to individuals who become HIV-infected while participating in the trial, or who test positive for HIV infection while being screened for trial participation
- The best process for ensuring that trial participants give informed consent and remain properly informed throughout the duration of the trial

Prevention Standards for Trial Participants

Researchers are obligated to minimize potential harms to research participants, and trials are not permitted to withhold proven HIV prevention interventions from trial participants. Recently, this obligation has raised a number of issues that need to be addressed:

- **Range of prevention services provided:** There is not yet consensus on the range of existing prevention methods that should be provided to participants in trials of new HIV prevention approaches. For example, several governments prohibit the provision of sterile injection equipment, a proven strategy for the prevention of HIV transmission among injection drug users.[75]
- **Quality assurance:** Although the basic principles of HIV prevention counseling are well established, the delivery of such counseling can vary widely in quality. For example, interactive, client-centered counseling appears to be more effective than didactic approaches.
- **Future changes in prevention standards:** As new HIV prevention methods are successfully developed, the obligations of trial sponsors may evolve. For example, if male circumcision is confirmed as an effective strategy for HIV prevention, it may need to be incorporated in the package of prevention interventions provided to trial participants or their partners. Because the addition of new prevention tools and strategies is likely to decrease the rate of new HIV infections in the study population, the number of participants in prevention trials may need to increase.

Recommendations

- **Guidance on prevention standards:** Trial sponsors and international agencies should convene a standing committee to provide timely guidance on the list of prevention interventions that have been proven in scientific studies to be effective in reducing the risk of HIV transmission, and should be provided to participants in prevention trials. Such a committee may be able to be linked to existing efforts, such as groups established as part of UNAIDS's Intensifying Prevention effort.[76]
- **Access to comprehensive prevention services:** Trial sponsors should ensure access for trial participants to all proven prevention services, given the local context, including, as appropriate, evidence-based prevention interventions for participants who are injection drug users. Funding from international donors—such as the Global Fund to Fight AIDS, Tuberculosis, and Malaria, and the U.S. government's President's Emergency Plan for AIDS Relief (PEPFAR)—should be used to support access to comprehensive prevention for clinical trial participants.
- **Monitoring:** Trial sponsors should work with communities and others to establish mechanisms to monitor and document the ongoing provision of prevention services.

Access to Treatment

In recent years, extensive debate has focused on the obligation of sponsors of HIV prevention trials to provide antiretrovirals and other HIV treatments to trial participants who contract HIV during a trial. Generally speaking, the initial debate over whether to provide antiretrovirals to trial participants who become infected has given way to discussions over how best to deliver the medications.[77]*

A consensus is emerging that antiretroviral provision is an indispensable part of the agreement between trial sponsors and trial participants. In exchange for the inconvenience and potential risks of participating in clinical research, many believe that participants have the reasonable expectation of receiving antiretroviral therapy if they become infected with HIV during the trial. In addition, many in the field view antiretroviral provision to trial participants as an obligation that is owed to the communities in which trials are conducted. Dramatic reductions in the price of antiretrovirals in developing countries, combined with the demonstrated feasibility of administering antiretrovirals in low-income countries, have also influenced the debates on the obligations to trial participants.

Ethical guidance for HIV vaccine trials released in 2000 by UNAIDS called for the provision of "care and treatment for HIV/AIDS and its complications" to participants who become HIV-infected during the trial, although the recommendations did not specify at that time the nature or duration of such an obligation.[78] In 2005, the International AIDS Society convened a meeting of stakeholders involved in pre-exposure tenofovir research to explore key issues associated with these trials, including access to antiretrovirals for trial participants who become infected.[79]

In recognition of the evolving discussion on this issue, UNAIDS is in the process of developing updated guidance on antiretroviral access and other issues associated with HIV prevention research. In addition, a number of trial sponsors have made arrangements with national HIV treatment programs to refer trial participants who become HIV-infected during the trial (see the discussion of treatment for HIV vaccine trial participants later in this section).

Key issues currently being debated and discussed regarding provision of antiretroviral treatment to participants in HIV prevention trials include:

- **Duration of obligation:** It must be assumed that antiretroviral therapy, once initiated, is likely to be needed for life. Yet no consensus currently exists on the appropriate timeframe for ensuring treatment for trial participants who become HIV-infected. It should be noted that participants who become HIV infected during a trial are unlikely to need antiretroviral treatment until five to 10 years after they become infected, complicating the practical implications of providing treatment to these trial participants.
- **Scope of obligation:** There is a lack of consensus about whether trial sponsors are obliged to ensure access to antiretrovirals for individuals who are screened for participation in a prevention trial but are found to be ineligible because they are HIV-infected. Current standard practice is to refer would-be participants who are excluded due to prior HIV infection to existing sources of care and support, although questions have been raised about whether it is ethical to conduct prevention trials where there are severe gaps in local capacity to provide HIV treatment and care. At the same time, others, especially those from settings in which treatment is not available or imminent, have urged that researchers not avoid their communities merely because antiretrovirals are not widely available.
- **Financial responsibility:** There is no clear agreement as to who should be responsible for covering the long-term costs associated with treatment of trial participants who become HIV-infected, especially in countries where treatment services are limited or do not exist. Funding is also needed for scaling up treatment services in the trial communities generally. If trial sponsors were to assume the financial costs and complexity associated with treatment provision, this would significantly increase the costs of prevention research. Some have proposed that an independent fund be established to cover costs of providing antiretrovirals and other care and treatment to individuals who become HIV-infected during trial participation, or who are found to be HIV-infected during a trial's screening stage.[80]
- **Community access:** In addition to arranging treatment access for trial participants, some have argued that the larger communities that host prevention trials should be prioritized for roll-out of broad-based treatment access.

Recommendations

- **Guidance on antiretroviral access:** Trial sponsors and international agencies such as UNAIDS and WHO should convene a broadly inclusive panel of experts—including clinical trial investigators, developing country health

* *It is important to note that people who become HIV-infected during the course of a prevention trial do not become infected from the investigational tool or strategy.*

ministries, trial sponsors, private industry, ethicists, affected communities, and people living with HIV—to develop guidance on key principles for the provision of antiretroviral therapy to individuals who become HIV-infected while participating in an HIV prevention trial, or who are found to be ineligible for the trial during the screening stage. This would include guidance on scope and duration of obligation, and financial responsibility.

- **Community access:** Where feasible and appropriate, communities that host prevention trials should be prioritized for introduction of antiretroviral treatment access. Provision of treatment to communities that host trials should be supported by international donors such as the Global Fund and PEPFAR.

Informed Consent

Informed consent requires (1) disclosure of critical information to potential trial participants, (2) comprehension by the potential participant of this information, and (3) the informed individual's voluntary choice to participate in the trial.[81] Although a participant's informed consent is typically obtained in writing on a consent form, informed consent should be viewed as an ongoing, interactive process that permits individuals to obtain and understand the information they need to make an informed decision.

In developing countries, where literacy rates are low and there may be little community experience with clinical trials, a major challenge is to ensure that participants understand basic facts about the trial before consenting to participate. Key issues include:

- **Presentation of information:** It has not been fully determined what amount of information should be provided, and in what manner, to ensure that consent is truly informed. For example, some prevention studies have incorporated visual images or group exercises into the informed consent process as a strategy to communicate risks, benefits, and other details regarding trial participation. However, there are no international standards for how information should be presented in order to obtain informed consent.
- **Verifying comprehension:** Ideally, researchers should be able to verify the individual's comprehension of critical information about the trial prior to enrollment, and throughout the trial. To date, most HIV prevention trials have included some strategy to measure comprehension, although optimal strategies to make such measurements remain unclear.

Recommendations

- **Guidance on informed consent:** Trial sponsors and international agencies should consult a broadly inclusive

HIV VACCINE RESEARCH AS A POTENTIAL MODEL FOR TREATMENT ACCESS

HIV vaccine trial sponsors have discussed for some time the ethical issues of providing antiretroviral treatment to participants who become infected with HIV during HIV vaccine clinical trials. In recent years, both the U.S. government-sponsored HIV Vaccine Trial Network (HVTN) and the International AIDS Vaccine Initiative (IAVI) have established policy guidance regarding the provision of treatment to volunteers who become infected with HIV while participating in their trials. This guidance provides a potential model for trials of other HIV prevention methods.

IAVI works with local partners to ensure the provision of long-term treatment and care, and in some cases, the partners assume responsibility for the costs of any needed care. If IAVI's partners are unable to do this, the organization commits to providing antiretroviral treatment for participants who become infected during a trial, for a period of five years after the start of treatment is clinically indicated.[82] Similarly, HVTN has pledged to provide "long-term" treatment to trial participants, although it has not specified a time-period for its treatment commitment.[83]

Both IAVI and HVTN have developed plans for ensuring access to treatment. IAVI has established an escrow account to pay for treatment needs in its trials, and HVTN has set up a foundation to fund treatment provision in its trials (HVTN is prohibited by U.S. law from providing treatment that is not the specific focus of research).

IAVI and HVTN acknowledge that providing treatment over the longer term will require establishing partnerships with governments, nongovernmental agencies, and communities. In a 2003 commentary in *The Lancet*, members of HVTN noted that while researchers cannot "reverse the global inequities" in HIV care they "can work with communities to develop, implement, and assess high-quality treatment models for participants in research programs, and encourage the development of sustainable community access to good HIV-1 care."[84]

panel of experts—including clinical trial investigators, developing country health ministries, private industry, ethicists, and affected communities—to develop guidance on key principles for informed consent in HIV prevention trials.

- **Assessment of comprehension:** All prevention trials should incorporate mechanisms for assessing trial participants' comprehension of information disclosed for purposes of obtaining informed consent. In addition to the participant's informed consent upon enrollment, assessments of comprehension and, as needed, re-education should occur periodically throughout the trial to ensure that understanding of key aspects of the trial does not diminish over time.
- **Community participation:** The Institutional Review Boards that oversee HIV prevention trials, as well as Community Advisory Boards, should include representatives of the communities from which trial participants are drawn, and people living with HIV. These community representatives can provide input into the substantive content of the information that should be disclosed to potential trial participants, interactive mechanisms for communicating key information, and strategies to maximize and monitor trial participants' comprehension. Trial sponsors should also undertake efforts to assist the communities from which participants will be drawn in understanding the basic nature of clinical research—including the purpose, benefits, and limitations of clinical research.
- **Best practices:** UNAIDS and WHO should work with trial investigators and sponsors to identify, define, and publish best practices with respect to informed consent in HIV prevention research.

ENGAGING COMMUNITIES IN PREVENTION RESEARCH

The communities in which prevention trials occur should be empowered to function as genuine partners with researchers and other stakeholders in conducting research that is vital to the fight against AIDS. Communities that host clinical trials must be educated about the research that is being conducted and be involved in all aspects of trial design and implementation. Moreover, community support is often vital to researchers' ability to enroll eligible individuals as trial participants, to successfully complete trials, and to eventually support roll-out of successful tools and strategies.

In recent years, community concerns about plans for large-scale studies of tenofovir for the prevention of HIV transmission were a major factor in the closing of two of the trials.[85] Although the concerns expressed about the tenofovir trials have varied, a common theme has focused on the degree to which researchers effectively engaged the communities in which trials would take place.[86]

In 2005, UNAIDS held a series of consultations on creating effective partnerships between HIV prevention researchers and civil society, which acknowledged there is a need "to define new approaches to collaboration that will facilitate critically important research while at the same time being responsible and accountable to community needs and priorities."[87] Key issues include:

- **Identification of "community":** Efforts to engage affected communities require researchers to define the community and determine who speaks on its behalf. In all instances, trial sponsors should forge strong relationships with national and district-level political and public health leaders. In addition, a May 2005 expert consultation convened by the International AIDS Society concluded that "community" includes "potential participants, domestic and international activists, non-governmental organizations, and human rights organizations."[88]
- **Nature and timing of community engagement:** Community engagement should extend beyond education and outreach to include the meaningful involvement of community representatives in Institutional Review Boards and/or Community Advisory Boards. Community involvement should begin well before trial recruitment begins. Community

representatives can have invaluable input regarding trial recruitment, informed consent, prevention counseling, and community relations.

- **Optimal strategies for engaging the community:** UNAIDS is in the process of developing guidelines on forging strong partnerships between affected communities and HIV prevention researchers. Potential strategies include retaining qualified staff to conduct community outreach, forging formal linkages with respected NGOs and community groups, and integrating community participation into Institutional Review Boards, Community Advisory Boards, and other institutions.

Recommendations

- **Strong community partnerships:** Sponsors of HIV prevention trials should build strong and genuine partnerships with the communities from which trial participants are drawn. Early community input should inform development of trial protocols, community education, and ongoing trial oversight.
- **Building research literacy:** Sponsors of HIV prevention trials should implement strong education programs to increase community awareness and understanding of the goals, nature, and purpose of planned research. This should also include reporting back to the community after the research has been completed.
- **Guidance:** International agencies such as UNAIDS and WHO should widely disseminate formal guidance on best practices for engaging communities.

3. PREPARING FOR ACCESS

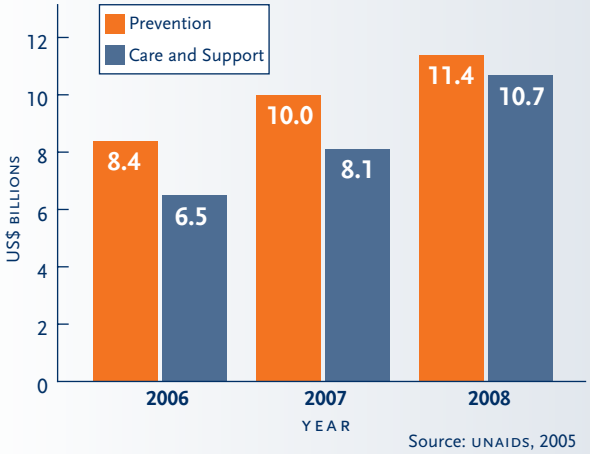
Given the global health imperative of curbing the AIDS epidemic, it is vital that the world rapidly introduce new HIV prevention methods after they prove effective in trials, and avoid the historic delays in making life-saving health interventions available to those who need them in poor countries. For example, for new vaccines for other infectious diseases, 15 years or more have typically passed after licensure to achieve even modest coverage in low- and middle-income countries.[89] There is considerable cause for concern in the case of new HIV prevention methods, since the global community has not yet succeeded in ensuring meaningful access to current interventions for HIV/AIDS, including both prevention and treatment services.[90]

While introduction of new HIV prevention methods poses significant challenges, particularly in developing countries, there are feasible strategies to address the obstacles. It is too late, though, to wait until after a new prevention method has been shown to be effective to take the steps needed to expedite introduction and uptake. To accelerate the implementation of new prevention methods, development of sufficient manufacturing capacity will likely need to begin years in advance, systems to purchase and deliver the intervention must be put in place, public health guidance must be developed, and national regulatory expertise may need to be strengthened. In many cases, extensive operations research will be needed to identify the best strategies and tactics for addressing these implementation challenges. In short, the world must act now to ensure that future prevention breakthroughs will be accessible to those who need them.

PREPARING FOR ACCESS— KEY RECOMMENDATIONS

- **Public health recommendations and regulatory capacity:** To avoid delays in rolling out new HIV prevention methods after they are shown to be effective in clinical trials, international agencies should maintain a standing committee to anticipate and provide needed guidance on new HIV prevention methods, and regulatory agencies in the United States and Europe should provide assistance to their counterparts in developing countries in evaluating new prevention methods.
- **Provider training:** The World Health Organization and others should develop provider training programs to promote the safe and proper use of new HIV prevention methods.
- **Preventing "disinhibition":** Because no new HIV prevention method will be 100 percent effective, strong, evidence-based communications and public education campaigns will need to accompany the introduction of new prevention methods, to prevent an inadvertent increase in risk behavior. It is essential that efforts to prevent behavioral "disinhibition" are monitored on an ongoing basis to ensure they are effective.
- **Resources for implementation:** Ensuring the rapid deployment of new prevention methods will require significant new resources, both to purchase new tools and to support programs such as the development of public health guidance, provider training, and community education. National governments and donors should commit to providing the resources necessary for the rapid roll-out of new HIV prevention methods, as part of a comprehensive response to the global epidemic that also prioritizes current prevention approaches and HIV treatment and care.

FIGURE 11. **Current Resource Needs for HIV/AIDS, Not Including New Prevention Methods**



Source: UNAIDS, 2005

Even if they are accessible, new HIV prevention methods will only have an impact on reducing the number of new infections if they are used by people at risk, and in combination with existing prevention tools. Introduction of new prevention methods must be accompanied by communications campaigns to encourage adoption of new approaches, and by educational initiatives to ensure that these prevention methods are used safely and properly.

It is also vital that strong, evidence-based education campaigns are undertaken to avoid complacency about risk behavior that could result from a mistaken belief that new interventions are 100 percent effective. If risk behavior increases, modeling studies suggest this could undermine rather than strengthen HIV prevention efforts, and actually result in a growth of new HIV infections. Efforts to introduce new tools must be accompanied by strong public health steps to reinforce the importance of current prevention methods, and ongoing monitoring and evaluation to ensure that these public health steps are in fact effective.

This section covers the following issues that are critical for expediting the introduction of new HIV prevention methods:

- Providing sound and timely public health recommendations regarding adoption of new prevention methods
- Developing public and provider education strategies to guide the safe and proper introduction of new prevention methods and prevent inadvertent increases in risk behavior
- Ensuring adequate resources and capacity to expedite introduction of new prevention methods
- Establishing strong, sustainable systems for monitoring and evaluation

PUBLIC HEALTH GUIDANCE

The availability of new HIV prevention methods could raise important policy questions. National decision-makers, as well as donors and international NGOs, will need to determine whether, and how, to integrate new HIV prevention methods into their health programs. In addition, public health guidelines must be developed to guide the safe and proper use of new prevention methods.

Guidance on use of new health tools is currently provided on an ad hoc basis. For example, in the case of initial efficacy results on male circumcision, informal discussions among key global health stakeholders resulted in consensus that additional studies should be completed before circumcision as an HIV prevention method could be recommended. In other instances, where consensus has been less clear, UNAIDS and the World Health Organization (WHO) have convened experts to advise on the proper public health approach to difficult questions. In some cases, these consultations have led to the development of formal public health guidance for use by national health ministries and other key stakeholders.[91]

To be effective, guidance on emerging prevention methods must be timely so that donors, national policy-makers, and program implementers can move swiftly to take advantage of new prevention approaches. Guidance must also be grounded in rigorous scientific evidence. Because several new prevention methods could be shown to be effective in the coming years, strengthening the capacity of national authorities, international agencies, and others to assess and introduce new prevention methods is an urgent priority. Furthermore, increasing capacity to develop and implement health policy on new health interventions will yield dividends beyond the fight against HIV/AIDS.

Recommendations

- **Timely guidance on emerging tools:** International agencies should maintain a standing committee to anticipate and assess the need for guidance on the introduction and proper use of new prevention approaches as they are shown to be effective in clinical trials. Such guidance should be based on the best available scientific evidence, and revised as new data and information become available—just as guidance on the optimal use of HIV treatment regimens is regularly reviewed and updated.

- **Building national and regional policymaking capacity:** Leading donors should support the long-term technical capacity of developing countries to develop

policies to guide the introduction and use of new health interventions, including new HIV prevention methods. As an intermediate step toward establishing sustainable national capacity, similarly situated countries in the same region or sub-region should collaborate in the development of public health policies regarding the introduction of HIV prevention methods that could emerge in the next several years.

- **Donor support for operations research:** In many cases, operations research will be needed to identify the best strategies and tactics for rolling out new prevention methods. International donors—such as the Global Fund to Fight AIDS, Tuberculosis, and Malaria, and the U.S. government's President's Emergency Plan for AIDS Relief—should commit funding specifically to support this operations research, and to assist countries in applying for such funding.

REGULATORY CAPACITY

To be eligible for use in a country, some new health technologies require the approval of the national regulatory authority. Technically sophisticated new HIV prevention methods—such as HIV vaccines, microbicides, and pre-exposure antiretroviral prophylaxis—will almost certainly require official licensure before they can be introduced in countries. Although WHO publishes a list of essential medications and pre-qualifies drugs and vaccines that meet accepted standards of quality, safety, and efficacy, the organization does not undertake a comprehensive regulatory review of new health products. Therefore, unless national regulators are prepared for the potentially complex issues that some new HIV prevention technologies are likely to present, significant delays could result in the introduction of new prevention methods. Key issues include:

- **Building national regulatory capacity:** Regulatory systems for drugs, vaccines, and medical devices are weak in most developing countries, potentially delaying the introduction and uptake of new health technologies. Historically, relatively few new health products have been designed for initial introduction in developing countries, and investment in strong regulatory infrastructure has not been viewed as a major priority in developing countries. To facilitate the rapid introduction of new products in countries where they are most needed, substantially greater national regulatory capacity must be built.[92]
- **Capitalizing on regulatory capacity in high-income countries:** Applicable laws, policies, and practices have historically barred regulatory authorities in high-income countries from undertaking regulatory review on behalf of another country or for products not intended to be used in the regulatory authority's home country. In recent years, however, a growing number of global health experts have advocated mechanisms to use the regulatory capacity in high-income countries to buttress regulatory systems in developing countries.
- **Unanswered scientific questions:** In the case of certain new HIV prevention technologies, such as microbicides and vaccines, there are unanswered scientific questions about what criteria should be used to make a decision regarding licensure—this applies to industrialized countries as well as developing countries.

Recommendations

- **Capacity building:** Leading donors should support sustained efforts to increase national regulatory capacity in developing countries. For new prevention technologies such as microbicides and vaccines, for which clear regulatory criteria for safety and efficacy do not exist, donors should also provide support to international agencies to convene appropriate regulatory experts to develop guidance for regulatory review.
- **Regulatory collaboration:** At the request of one or more developing countries, the U.S. Food and Drug Administration (FDA), European Medicines Evaluation Agency (EMEA), and other leading regulatory bodies should be prepared to undertake a regulatory review and analysis of a complete regulatory submission regarding new health interventions intended for primary use in developing countries, including new HIV prevention methods. Upon completion of the review or analysis, the regulatory body would provide the requesting party with a summary of findings, with ultimate licensure decisions remaining the province of national regulatory authorities in countries where the new tool or strategy will be used. FDA, EMEA, and other leading regulatory bodies should set aside sufficient budget to support such regulatory reviews.

  It should be noted that under a new initiative by EMEA, European regulators will, at the request of a developing country, review and analyze regulatory submissions for new health products that are designed

for primary or exclusive use in developing countries. Under this new policy, licensure of any new product ultimately remains the province of individual national regulatory authorities.[93]

- **Regional collaboration:** Regional collaboration among national regulators could strengthen the ability of developing countries to expedite the review and approval of promising new HIV prevention methods. By pooling regulatory expertise, regions could capitalize on available capacity to accelerate the introduction of new products. Supported by donors, regulatory bodies in different regions should develop strategic plans for timely, collaborative review and information-sharing regarding new HIV prevention methods that are candidates for licensure.
- **Harmonization:** International efforts to harmonize regulatory requirements for new health interventions should be broadened to include national regulatory authorities from developing countries. Although national regulatory agencies in North America, Europe, and Japan have worked under the umbrella of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use to reduce the duplication and expense associated with regulatory approval in multiple countries, this process has yet to address regulatory processes in developing countries.[94]

PUBLIC AND PROVIDER EDUCATION

Effective communication and education strategies are vital to the introduction of new HIV prevention tools and strategies. Individuals will not adopt a new prevention method if they are not aware of it, and sustained marketing efforts may be needed to promote uptake of some new methods. In addition, training may be required—for providers as well as consumers—to ensure that new prevention methods are used properly. Most importantly, strong, proactive communication and education strategies will be essential to ensure that the introduction of new prevention methods does not inadvertently lead to overall increases in sexual risk behavior.

Community Education and Marketing

Proof in clinical trials that a new prevention method, such as male circumcision, is safe and effective will not automatically result in its widespread adoption by consumers or providers. And if individuals who adopt a new prevention method use it improperly, this could diminish its effectiveness in reducing the risk of HIV transmission.

For example, studies indicate that education and experience using condoms significantly reduce the likelihood of condom failure.[95] As new HIV prevention methods emerge, community education initiatives will be needed to raise awareness of the new method and to encourage its adoption and proper use. Social marketing approaches to community education have proven to be highly effective in increasing consumer adoption of new health products.[96]

Acceptability studies can inform efforts to ensure broad and correct adoption of new prevention methods. Developers of candidate microbicides, for example, have performed extensive research on the acceptability of the products among sexually active women and their male partners.[97] In the case of male circumcision, surveys and anecdotal data indicate widespread demand for circumcision in some parts of Africa,[98] although there is a need for further research, given strong cultural norms and practices surrounding circumcision in many countries. And in Zimbabwe, researchers conducted a female diaphragm acceptability study,[99] and are continuing to assess acceptability by the community and providers while they test the diaphragm's effectiveness for HIV prevention.

Recommendations

- **Acceptability studies:** Sponsors of efficacy trials of new HIV prevention methods should undertake studies to assess the acceptability of the method to consumers and, when appropriate, to their sexual partners. These studies should also assess acceptability among providers.
- **Financing:** Additional donor financing for new prevention methods should include funding for community education initiatives and social marketing campaigns to identify and implement strategies to encourage adoption and proper use of new prevention methods.

Preventing Behavioral "Disinhibition"

It is critical that the introduction of new HIV prevention methods does not inadvertently lead people to become complacent about risk behavior.[100] If the introduction of a new prevention method is accompanied by an overall increase in risk behaviors, the protective benefits of the new method, as well as of other prevention measures, may be canceled out. In the most extreme case, a "disinhibiting" effect of a new prevention method could result in an actual increase in the number of new HIV infections. The need to address potential disinhibition as a result of prevention advances is especially important for the classes of prevention methods currently under development, as all would offer only partial protection against infection. Key issues include:

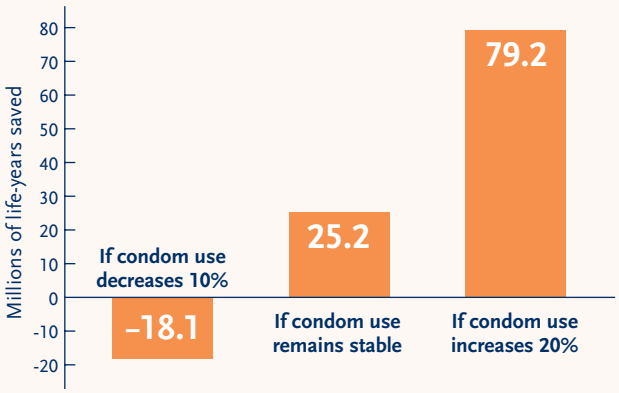
- **Community education:** Integration of new prevention methods into national AIDS programs should be accompanied by strong, sustained campaigns to educate affected communities regarding the benefits and limitations of the new methods. These campaigns must be grounded in rigorous scientific evidence of effectiveness. Both donors and national authorities should understand that the costs of introducing new prevention methods include substantial investments in education to avoid disinhibition.
- **Monitoring of behavioral changes:** To inform public health measures to prevent disinhibition, behavioral surveillance will be needed to assess the effect, if any, of new HIV prevention approaches on risk behavior decision-making. Currently, behavioral surveillance systems are extremely weak in many developing countries.

BEHAVIORAL DISINHIBITION—LESSONS FROM TREATMENT ACCESS

As new HIV prevention methods are introduced, it is critical to ensure that risk behavior does not increase as a result of complacency about HIV. Researchers have modeled the impact of even small increases in risk behavior as the result of expanded treatment access, which could also have a "disinhibiting" effect on risk behavior.

For example, in India, projections by the World Bank estimate that even small decreases in condom use as a result of expanded access to treatment could actually result in a loss of millions of life-years. However, if treatment access is accompanied by strong prevention campaigns, and condom use remains stable or increases, expanded access to treatment and prevention together could save millions of life-years.

FIGURE 12. **Risk Behavior, Treatment Access, and Life-Years Saved in India**



Source: M. Over et al., 2004

Recommendations

- **Education campaigns:** It is essential that the introduction of new prevention methods be accompanied by strong, sustained, well-financed public education campaigns that warn against disinhibition, emphasize the benefits and limitations of new prevention methods, and encourage use of the full range of proven prevention measures, including sexual abstinence, partner reduction, and condoms. The development of these campaigns should be informed by social science research to identify the most effective education strategies.

- **Technical support:** WHO, the Centers for Disease Control and Prevention, and other leading public health agencies should enhance their technical support to countries to improve behavioral surveillance systems for detecting potential disinhibiting effects of new prevention methods. Donors should prioritize financial assistance to countries to strengthen public health surveillance and the development of effective public education campaigns regarding new HIV prevention methods.

Provider Training

As new HIV prevention methods are successfully developed, health care providers and community workers will require training in the proper use of new prevention approaches. In many developing countries, for example, few health care providers have experience in circumcising adult males, and when circumcision is improperly performed, the procedure can result in serious medical complications or death. The problem of health worker training is compounded by the fact that many developing countries suffer acute shortages of qualified health care personnel in general.

Recommendation

- **Training:** With targeted financial support from donors, WHO should develop regional and country-level training measures to promote proper use of new HIV prevention methods. In some cases it may be advisable to implement accreditation and supervision programs, although such efforts would need to account for the fact that in many countries, traditional healers and religious leaders play a critical role in providing and advising on health care.

SUPPLY AND DELIVERY

Substantial financial investments will be needed to build the long-term capacity essential for ensuring the adequate supply and swift delivery of new HIV prevention methods in developing countries.

Procurement and Supply Management

Some new HIV prevention methods will present significant procurement and supply management challenges for the developing countries most seriously affected by HIV. In the case of technically sophisticated prevention methods—such as HIV vaccines, microbicides, and antiretrovirals for prophylaxis—the cost of the new prevention methods will likely substantially exceed most countries' ability to purchase them. In countries where annual per capita health spending is especially constrained, even inexpensive prevention options will compete with other national priorities for budget allocations. In addition, recent experience in the introduction of antiretrovirals for the treatment of HIV underscores the potential for logistical issues to impede introduction of life-saving health interventions, as countries have found that roll-out of HIV treatment requires the capacity to forecast demand and manage supplies on a large scale.[101]

In addition to the need for increased and sustained political commitment to provide resources to purchase and deliver new prevention methods, key issues include:

- **Estimating demand:** Ensuring sufficient supply and, if necessary, manufacturing capacity for new HIV prevention methods requires accurate demand forecasting. Future demand for new HIV prevention methods will depend on a variety of variables, including existence of a means to purchase the product, accessible delivery systems, and consumer acceptance, among other factors. Demand is not static and can be influenced by external factors, such as donor assistance and social marketing.

- **Country-level systems for procurement and supply management:** Limited or non-existent national capacity to manage the purchase, delivery, and inventory of health commodities has limited countries' ability to rapidly expand access to antiretroviral therapy in recent years. Similar impediments could slow uptake for new prevention methods, although experience gained through the global push for universal HIV/AIDS treatment access is rapidly helping countries build

capacity and expertise that will assist in expediting introduction of new prevention methods.

Recommendations

- **Political commitment to provide resources:** Both developed country donors and developing country leaders should honor the commitments made at the United Nations General Assembly Special Session on HIV/AIDS[102] to support the rapid introduction of new methods for the prevention of HIV transmission. In addition, further action is needed on measures currently being examined to increase resources for international health and development, including advance purchase mechanisms for new prevention methods,[103] use of securities markets to generate funds for health and development initiatives (e.g., the International Finance Facility for Immunization),[104] and implementation of a tax on air travel.[105]
- **Pricing agreements:** With the close cooperation of developing countries and multilateral institutions, leading donors should implement, monitor, and refine new mechanisms to purchase new prevention commodities at favorable prices for developing countries.
- **Capacity building:** Countries should receive targeted support to build the capacity to develop timely analyses of future demand for emerging HIV prevention methods such as microbicides and to implement sound purchase, delivery, and supply management systems for new prevention methods.

Manufacturing Capacity

For technologies such as HIV vaccines and microbicides, several years can be required to build sufficient production capacity, and manufacturers may need to make decisions regarding initial manufacturing capacity in advance of initial regulatory licensure—that is, before large-scale efficacy trials have been completed.[106] Even for less complicated technologies, it is often challenging to gauge future demand and to calibrate manufacturing capacity to meet anticipated demand. Key issues include:

- **Creating and sustaining sufficient manufacturing capacity:** Even for relatively simple technologies, construction of manufacturing capacity to meet global demand involves substantial financial outlays and adherence to regulatory requirements. In many cases, owners of new prevention technologies are small biotech companies, academic centers, or not-for-profit organizations that have limited access to capital.

Recommendation

- **Innovative mechanisms for ensuring sufficient manufacturing capacity:** Leading donors, multilateral organizations, and developing countries should collaborate in the development of strategies to ensure timely and sufficient manufacturing capacity to meet global demand for a wide variety of new HIV prevention methods.

MONITORING AND EVALUATION

A key role of regulatory agencies in developed countries is to monitor health interventions after they are approved for use. Such monitoring helps to document the impact of new tools and strategies, detect side effects not identified in clinical trials, and refine public health guidelines for optimal use of health interventions. In the case of side effects, for example, use of improper circumcision techniques by untrained practitioners can result in severe infections, permanent disability, and even death, underscoring the need for strong quality assurance mechanisms.

At the same time, documentation of the public health impact of new interventions will help generate momentum for investment in even better tools and strategies for the future.

Recommendation

- **Quality assurance:** Additional donor financing for new HIV prevention methods should include sufficient support for the implementation and maintenance of strong national monitoring, evaluation, and quality assurance programs. These programs should include components that monitor for potential disinhibiting effects of new HIV prevention methods.

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