



# ALLIANCE FOR MICROBICIDE DEVELOPMENT

**02 March 2007, Volume 8, Number 8**

The Alliance for Microbicide Development *News Digest* is an **unedited** compilation of:

- Media coverage of microbicides;
- Abstracts of articles on microbicides and relevant science in peer-reviewed journals;
- Material on other reproductive health and HIV prevention technologies, including HIV vaccines; and
- Matters of policy and politics with importance for microbicide research, development, and advocacy.

Its purpose is to:

- Raise awareness around the range of opinions and information about microbicides disseminated in the press and scientific journals; and
- Provide a neutral, objective basis for decision-making and evidence-based advocacy.

The *News Digest* is produced in a web-based format. Readers can view individual articles or complete issues at <http://www.microbicide.org/publications/> and may also search by keyword for articles included in issues of the *Digest* created after 27 January 2006, at <http://www.microbicide.org/publications/search.html>. Should you wish to be removed from the *Digest* distribution list, please advise us at [digest@microbicide.org](mailto:digest@microbicide.org). We welcome comments, questions, and ideas about other microbicide-relevant topics we might cover, services we might provide, and better ways of providing them!

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### 1. MONTHLY MICROBICIDE PIPELINE UPDATE

#### March 2007

Each month, the *Digest* includes an update on overall progress in the field. Currently, there are 11 **microbicide** candidates in clinical development and over 30 in preclinical development. As a continued effort to maintain the most up-to-date information, we urge you to visit the Alliance website at [www.microbicide.org](http://www.microbicide.org) or contact Carolyn Plescia, Alliance Writer/Research Associate, by email ([cplescia@microbicide.org](mailto:cplescia@microbicide.org)) or by phone (301-587-3302) with any updates, questions, or comments.

#### MICROBICIDES IN ONGOING AND PLANNED CLINICAL TRIALS

March 2007

<i>Candidate</i>	<i>Mechanism of Action</i>	<i>Developer</i>	<i>Phase*</i>
ACIDFORMA/Amphora	Vaginal defense enhancer	CONRAD; Instead, Inc.	1
BufferGel®	Vaginal defense enhancer	ReProtect, Inc.	2/2B

Carraguard <sup>®</sup>	Entry/fusion inhibitor	Population Council	3
Dapivirine (TMC120)	Replication inhibitor	International Partnership for <b>Microbicides</b> (IPM)	1/2
Invisible Condom <sup>™</sup>	Entry/fusion inhibitor	Laval University	1/2
PC 815 (Carraguard <sup>®</sup> and MIV-150)	Combination	Population Council	1
Praneem polyherbal vaginal tablet	Uncharacterized mechanism	Talwar Research Foundation	2
PRO 2000	Entry/fusion inhibitor	Indevus Pharmaceuticals, Inc.	3
Tenofovir/PMPA gel	Replication inhibitor	CONRAD; IPM	2B
UC-781	Replication inhibitor	CONRAD	1
VivaGel <sup>™</sup> /SPL7013	Entry/fusion inhibitor	Starpharma Ltd.	1

### AMDC Alliance for Microbicide Development

*\*Some candidates are in more than one phase of clinical testing. The phase listed in this table represents the most advanced clinical trial currently planned or underway for each candidate. (This table does not include trials of contraceptive efficacy). For modifications, please contact Carolyn Plescia, email [cplescia@microbicide.org](mailto:cplescia@microbicide.org), tel. 301-587-3302.*

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## 2. ALLIANCE UPDATES AND COMMUNITY NEWS

### Alliance coverage of the 14th Conference on Retroviruses and Opportunistic Infections

At the beginning of next week, the Alliance will produce a *News Alert* dedicated to the *14th Conference on Retroviruses and Opportunistic Infections* (CROI), which was held 25-28 February 2007 in Los Angeles, California, USA. The *Alert* will include a list of abstracts of **microbicide**-relevant research presented at the conference as well as a compilation of **microbicide**-relevant media coverage of CROI.

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## 3. MEDIA COVERAGE OF MICROBICIDES

### "Scientists rethink approach to HIV gels"

**Date:** 01 March 2007

**Source:** *Nature*. Vol 446, No 7131.

**Author(s):** Erika Check

Scientists and activists struggling to combat the HIV epidemic were shattered by last month's failure of a candidate **microbicide** gel in large clinical trials. **Microbicides** aim to block HIV infection, but the candidate product - cellulose sulphate - seemed to increase women's susceptibility. In the wake of this setback, some are now warning that the field must change its approach.

Dozens of candidate **microbicides** are being tested in labs around the world. But advocates of change say the field must make hard choices about which of these should graduate to phase III clinical trials - extended trials to confirm that a product works - because these trials are expensive and time-consuming. Such choices have not previously been made: the gels tested so far were the first to be ready, not necessarily the most promising.

"How many more clinical trials are we going to be able to do with dramatic failures like this?" asks Ronald Veazey, chair of the division of comparative pathology at the Tulane National Primate Research Center in Covington, Louisiana.

The **microbicides** tested in phase III trials so far all belong to a 'first generation' of products that aim to make the vagina less hospitable to HIV, but don't target the virus directly. So far, none of these has worked. One, Savvy gel, failed, and two - cellulose sulphate and the spermicide nonoxynol-9 - led to higher HIV infection rates. Phase III trials of three other products are ongoing, a redundancy that is now unavoidable as the trials have already begun.

Meanwhile, most researchers see more promise in a batch of **microbicides** at an earlier stage of development. These products contain gel formulations of antiretroviral drugs that target HIV. But for these **microbicides**, too, there are many similar products in the pipeline.

For instance, different groups are testing at least four **microbicide** candidates belonging to a class of drug known as non-nucleoside reverse transcriptase inhibitors (NNRTIs). Two of these will probably be ready for phase III trials before 2009. The question now is whether all the products should automatically be pushed into such trials.

"Are we really going to proceed with two different NNRTIs, or should we be doing a study comparing them head-to-head, to help us determine which move forward?" says Salim Abdool Karim, director of an AIDS research centre at the University of KwaZulu-Natal in Durban, South Africa.

Right now, it is difficult to choose the best candidates without doing large human studies because different research groups use different preclinical testing methods, and there is no agreement on which of these tests best predict how a **microbicide** will act in patients.

The failure of cellulose sulphate may actually help solve this problem. CONRAD, the Virginia-based agency that organized trials of cellulose sulphate in five countries, is determined to find out why the compound was harmful. "We'll probably put together a blinded panel of compounds, including cellulose sulphate, and send it out to various individuals working on different models and see if they can come up with any clues," says Henry Gabelnick, CONRAD's executive director. Testing the same products across different models could help researchers compare different **microbicides** in future.

But that will leave a bigger obstacle: each research group is investing in its own product, so will be reluctant to step aside for others. The field may need a guiding hand from an impartial body, which doesn't exist at the moment.

It has been suggested that a working group on **microbicides** currently being set up by the US National Institutes of Health's Office of AIDS Research may serve this role. Its composition and role have not been clearly defined, but advocates suggest it could solicit advice from independent experts about which products should proceed to clinical trials.

Some, including Gabelnick, say it would be a mistake to jettison products just to avoid redundancy. "We don't know enough to say these are all the same," he argues.

But others, such as Polly Harrison, director of the Alliance for **Microbicide** Development based in Silver Spring, Maryland, say someone has to help the field reach a consensus. "Prioritization has to occur, and it has to go all the way along the pipeline," Harrison says. "We know we need this."

### "Trial and failure"

**Date:** 01 March 2007

**Source:** *Nature*. Vol 446, No 7131.

**Author(s):** Editorial

Last month saw the failure of a clinical trial of a cellulose sulphate **vaginal gel** as a protective measure against HIV infection (see page 12). The result was a disappointment for **microbicide** researchers, and a setback for millions of women in Africa and elsewhere who could benefit from such a product. The international trial, organized by CONRAD, a reproductive-health research group based in Virginia, ended when the gel in question was found not only to be ineffective, but actually to increase the risk of HIV infection.

This is the third large-scale clinical trial of a **microbicial** gel for AIDS protection to fail. Naturally, it leaves researchers asking where the approach will go from here. Some counsel patience: the development of new therapies is always an arduous and unpredictable process, they argue.

The concept of **microbicide** gels--one of the few interventions that might allow women to protect themselves from HIV infection--has been heavily promoted by activists, particularly in the United States. Buoyed by success in raising awareness and funds, these activists want to see the product pipeline filled with as many reasonable candidates as possible.

But a continued pattern of well-publicized trial failure carries risks. This has been amply demonstrated by the history of AIDS vaccine research, where failed trials of products that hadn't even done well in animal models did little to further the development of a working vaccine. And when different groups push their favourite products into trials without taking a hard, rational look at which are most likely to succeed, the whole enterprise suffers. Multiple failures lead to a loss of public confidence. Even if donors continue funding the work, it becomes difficult to recruit volunteers for clinical trials if people think the product is doomed to failure--or worse, that it might even harm their health.

The **microbicide** field therefore requires a mechanism to help it make rational choices about the best candidates to move through trials. The field is already good at exchanging information. As part of this process, leaders and funders of **microbicide** clinical trials meet twice a year and are considering doing so more often. But they are not in the business of filtering late-stage trial candidates.

Participants need to explore ways of doing just that, however. Researchers, activists and funders of **microbicide** work should construct a consultative body that will have the confidence of the community, and help it reach a consensus on issues such as how best to test for efficacy and safety in animals, and how to use the results from such tests to move the best **microbicide** candidates into large human studies.

Ideally, this should be part of a wider discussion on how to test and roll out interventions to prevent AIDS. Several groups have recommended that researchers convene a cross-community forum to discuss issues related to all the concepts now in trials: prophylaxis with oral antiretroviral drugs; barrier methods initiated by women; treatment of HIV-infected patients who have non-infected partners; vaccines; **microbicides**; and male circumcision and herpes suppression, which both got a boost from positive trial results last week.

Such a discussion could also help researchers address common problems, such as how best to accommodate the high pregnancy rates in trial populations (which tend to disrupt trials, as pregnant women withdraw from them), and the fact that when counselling is provided in trials of new interventions, the rate of HIV infection plummets, potentially obscuring the effect of the intervention. Researchers also have a common interest in working out how to ensure that interventions that prove to be successful end up being used where they are most badly needed.

Researchers are supportive of such cross-community discussion. At the XVI International AIDS Conference in Toronto last August, for example, a group of about 50 researchers and activists known as the Global HIV Prevention Working Group laid out its own blueprint of challenges for AIDS prevention. On 23 February, the Forum for Collaborative HIV Research released a report that echoed the working group's findings. And a panel of the US Institute of Medicine will report later in the year on the challenges facing clinical trials of interventions to prevent HIV. There is broad and diverse agreement on the urgent need for cross-disciplinary dialogue on these questions. But all the talk must lead to active and careful coordination of AIDS prevention research, to confront the pandemic.

### **"Setbacks, achievements mark history of AIDS, speaker at U. Penn says"**

**Date:** 28 February 2007

**Source:** *Daily Pennsylvanian*

**Author(s):** Julie Cohn

Despite 1,000 people dying every day in South Africa from AIDS, international response is moving at a snail's pace.

Stephen Lewis, former United Nations ambassador, deputy executive director of UNICEF and special UN envoy for HIV/AIDS, spoke at Tuesday's University of Pennsylvania Global Forum about both the many setbacks and achievements with regard to the disease and its spread throughout Africa. "What is it about Africa? How can we let millions of people be considered expendable?" asked Lewis, who has more than 25 years of experience handling the issues of HIV/AIDS in Africa.

Lewis suggested a "subterranean racism" is responsible for the slow international response to the pandemic. However, Lewis said he was hopeful for future success in Africa, citing recent scientific breakthroughs. "It is fair to say we're at least a decade away from developing the vaccine for HIV/AIDS," Lewis said, but he added that scientists are working on topical ointments called **microbicides** that, when vaginally applied, should prevent infection. One of the most successful methods of preventing the spread of HIV is male circumcision, which Lewis said has a 30-to 60-

percent success rate in preventing disease transmission.

For Lewis, these new technologies cannot come soon enough. He shared a number of statistics pointing to the devastation caused by HIV/AIDS of the African population. For example, a growing number of motherless youths now live in households run either by the eldest offspring, often as young as 12 or 14, or with grandmothers, a shift that is redefining the structure of the family. Lewis urged Penn students to get involved, suggesting they join one of the major NGOs: Act-Up Philadelphia, Save the Children, Care or World Vision.

Many Penn administrators attended the event, including Provost Ron Daniels and Dean Dennis DeTurck, who also encouraged students to take advantage of Penn's travel abroad program in Africa. Junior Rachel Conrad, a health and society major who attended the lecture, is currently preparing to study in Botswana. Penn medical students have also recently been interning in Botswana, contributing to relief efforts and progress in the area.

Junior Katie Wolff commented that Lewis "did a really good job emphasizing what needs to be done without being depressing."

"The lecture was great," said law school student Mariam Jabyn. "I came here to know more about Africa and the response to HIV, and I learned a lot."

"His talk was persuasive, without being overbearing," Conrad said. "I can't wait to be involved next year."

### "Meharry will go forward in testing AIDS-preventing 'chemical condom'"

**Date:** 26 February 2007

**Source:** *Tennessean.com*

**Author(s):** James E. K. Hildreth

<http://www.rctimes.com/apps/pbcs.dll/article?AID=/20070226/OPINION03/702260330/1007/MTCN0305>

*The views expressed here are those of James E. K. Hildreth, M.D., Ph.D., professor and director of the Center for AIDS Health Disparities Research at Meharry Medical College.*

Meharry Medical College's intensive drive to develop a "chemical condom" for woman-controlled HIV prevention took on added urgency a few weeks ago when two U.S.-based international research organizations pulled the plug on their separate, late-stage clinical trials of a potential **microbicide**. Despite this development, Meharry researchers are still preparing to launch AIDS prevention trials to establish the effectiveness in humans of another **microbicide** candidate that has shown great promise in animal studies.

CONRAD, a reproductive health research organization in Northern Virginia, surprised the global health community with its announcement Jan. 31 that a Phase III clinical trial of its AIDS-prevention gel - cellulose sulfate, or UsherCell - would end immediately. The reason: CONRAD noted an increase - not a decrease - in HIV infections among female study participants. On the same day, Family Health International of Research Triangle Park, N.C., halted its study of the same chemical compound even though its Phase III prevention trials did not detect similar dangers.

Both research teams deserve applause. Immediately upon learning of an apparent danger, they halted their studies and offered full public disclosure of the reasons why. That is good science, even though the hoped-for solution has not

yet been found. What an anxious public needs now is background, perspective and truth. Scientists have struggled for years to develop an HIV vaccine or a cure for AIDS. But HIV has been a moving target, and our current understanding is that an effective, preventive vaccine may be a long way off.

A **microbicide** - used as a cream, gel or sponge - is placed directly on the body or in the vagina or rectum. Like antibiotics that destroy bacteria, an effective HIV **microbicide** kills the virus before it can infect a person's cells. At the present time, **microbicides** represent the best short-term hope for slowing and/or preventing the spread of AIDS.

The Center for AIDS Health Disparities Research at Meharry Medical College is developing a very promising **microbicide** based on a chemical called betacyclodextrin. It strips cholesterol off infected cells, keeping virus from being released; strips cholesterol from uninfected cells, keeping the virus from entering; and strips cholesterol from the virus itself, preventing its entry into cells. Betacyclodextrin has been studied extensively in animals and humans and has a well-established safety profile. It is already routinely used, for example, in mouthwash, eyedrops, for added flavoring in food, in topical creams and intravenous drugs.

Betacyclodextrin is not the only other compound under study. More than 50 **microbicides** are still being evaluated, many of which show great promise. The world community needs to know that the intense effort to develop an HIV **microbicide** continues - and should continue - despite the end of the CONRAD and FHI studies.

### "UH seeks women to test HIV-protection products"

**Date:** 25 February 2007

**Source:** *Plain Dealer (Cleveland)*

**Author(s):** Regina McEnery

<http://www.cleveland.com/medical/plaindealer/index.ssf?/base/news/1172396267301350.xml&coll=2>

University Hospitals Case Medical Center is looking for women to participate in the region's first studies of **microbicides**, which are topical creams and lotions that can be applied before intercourse to protect against HIV.

With an estimated 16 million women worldwide living with the human immunodeficiency virus, the global public health community is eager to find alternative methods of prevention. About three-quarters of the women with HIV -- the virus that causes AIDS -- live in sub-Saharan Africa, where condom use is still controversial.

University Hospitals, the leading clinical affiliate of the Case Western Reserve University School of Medicine, will be part of a national network testing vaginal products designed to block transmission.

UH hopes to enroll women by the summer but is still reviewing which experimental products to test, said Dr. Michael Lederman, director of the Center for AIDS Research at Case and a principal investigator of UH's AIDS Clinical Trials Unit.

Lederman leads an international group that developed a compound to prevent vaginal transmission of HIV in monkeys. The drug shuttered the molecular receptors that simian HIV needs to get inside cells. The group hopes to develop a less-expensive cousin of the compound, but human tests are at least a year away, Lederman said.

Although dozens of **microbicides** are in development, the field has been littered with failures. Most of the first-generation antiviral drugs for women relied on a detergent-like substance to burst the protective covering surrounding HIV cells. The products were uncomfortable and performed poorly in trials.

Last month, two international **microbicide** studies were halted after research suggested that the gel might actually increase the risk of infection in women.

Lederman said the **microbicide** field is evolving and he is optimistic that compounds like his, which target specific mechanisms in the transmission of HIV, will lead to better prevention methods.

Women interested in volunteering for **microbicide** studies can contact Robert Bucklew at the AIDS Clinical Trials Unit, at 216-844-2247. All information will be kept confidential.

The AIDS Clinical Trials Unit at UH also will open a satellite in Uganda to join federally funded studies of new AIDS therapies. Only a handful of units operate in Africa, home to about 60 percent of the 39 million people worldwide living with HIV/AIDS.

Case and its collaborators at the Joint Clinical Research Centre in Kampala, Uganda, will look at the long-term effects of the AIDS drug nevirapine. The drug has been a powerful tool in preventing the transmission of HIV from pregnant women to their unborn children, but infected women develop resistance to the drug quickly.

The international unit also plans studies in the management of patients infected with both HIV and tuberculosis, the most common opportunistic infection among AIDS patients in sub-Saharan Africa. And the unit will look at cheaper methods of monitoring patients on life-prolonging AIDS therapies.

Case's expansion occurs at an otherwise unsettled time for government AIDS research. The National Institutes of AIDS and Infectious Diseases, which doles out most of the public grants, has significantly scaled back support for clinical-trials units, most of which are based at teaching hospitals.

About 10 units will receive no additional money, while others, like Cleveland's, will get less, Lederman said. The National Institutes of Health renewed Cleveland's grant to run the unit for seven years, awarding \$2 million for the first year. The yearly stipends could fluctuate after that, Lederman said.

The cutbacks reflect the overall state of government research dollars, which have declined for the first time in about a decade.

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#### **4. PUBLISHED RESEARCH: MICROBICIDE-SPECIFIC**

**"Structural studies of algal lectins with anti-HIV activity"**

**Author(s):** Ziolkowska NE, Wlodawer A

**Reference:** N/A 53(4):617-26.

**Published Abstract:** A number of antiviral lectins, small proteins that bind carbohydrates found on viral envelopes, are currently in pre-clinical trials as potential drugs for prevention of transmission of human immunodeficiency virus (HIV) and other enveloped viruses, such as the Ebola virus and the coronavirus responsible for severe acute respiratory syndrome (SARS). Lectins of algal origin whose antiviral properties make them candidate agents for prevention of viral transmission through topical applications include cyanovirin-N, Microcystis viridis lectin, scytovirin, and griffithsin. Although all these proteins exhibit significant antiviral activity, their structures are unrelated and their mode of binding of carbohydrates differs significantly. This review summarizes the current state of knowledge of the structures of algal lectins, their mode of binding of carbohydrates, and their potential medical applications.

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## 5. PUBLISHED RESEARCH: RELEVANT BASIC AND TRANSLATIONAL SCIENCE

### "Putting sexuality (back) into HIV/AIDS: Issues, theory and practice"

**Author(s):** Boyce P, Huang Soo Lee M, Jenkins C, et al

**Reference:** N/A 2(1):1-34.

**Published Abstract:** After more than twenty years of programming and activism aimed at stemming the sexual transmission of HIV (and addressing the needs of those most vulnerable to infection) the HIV/AIDS epidemic continues to grow worldwide. Taking up this concern, this paper argues that one of the reasons why HIV prevention has had limited success is because of inadequate conceptualization of human sexuality in such work. Giving sexuality a more prominent position in responses to the epidemic raises a range of issues, including theorization of gender, understanding of sexual subjectivity, the significance of pleasure (or lack of pleasure) in sexual decision-making, and conceptualization of sexual behaviour and culture. Taking these themes forward entails asking significant questions about the underlying paradigmatic and methodological commitments of mainstream HIV/AIDS research, especially the tendency to reproduce accounts of human sexuality as if it were a measurable form of conduct only. Advocating new approaches that take the meaning and symbolic value of sexualities into account complicates established orthodoxies in the field whilst offering potential for more effective HIV prevention strategies.

### "T-lymphocyte profile and total and virus-specific immunoglobulin concentrations in the cervix of HIV-1-infected women"

**Author(s):** Quayle AJ, Kourtis AP, Cu-Uvin S, et al

**Reference:** N/A 44(3):292-8.

**Published Abstract:** BACKGROUND: The mucosal lymphocyte population is the largest in the body, and the gastrointestinal compartment has been well characterized in HIV infection. Much less is known about the effects of HIV on the genital tract. OBJECTIVE: To examine the T-lymphocyte phenotype and receptor repertoire as well as total and virus-specific immunoglobulin concentrations in the endocervix of HIV-infected women at different stages of infection as compared with uninfected women. PATIENTS AND METHODS: Participants were 12 seronegative

women, 10 HIV-infected "slow progressors" not taking antiretroviral therapy, and 9 HIV-infected women whose antiretroviral therapy was failing. We used multiparameter flow cytometry to enumerate T-cell populations on cytobrush-obtained cervical specimens, the immunoscope technique to determine the T-cell receptor (TCR) repertoire, and quantitative enzyme-linked immunosorbent assays for antibody determinations on cervical secretions absorbed onto ophthalmic sponges. Nonparametric statistical analyses were performed. RESULTS: We found marked depletion of leukocytes and CD4 T lymphocytes in the endocervix of HIV-infected women as compared with uninfected women; this was significant at more advanced disease stages. Naive T cells were rare in the endocervix of all groups. Activation marker expression was higher in endocervical T lymphocytes than in peripheral blood among control and slow-progressing HIV-infected women but not in women failing therapy. Endocervical T lymphocytes showed highly restricted utilization of Vbeta TCR families. Unlike other mucosal sites, the cervix contained IgG as the predominant immunoglobulin isotype. HIV-IgG was detected in the cervix of most HIV-infected women and in blood of all infected women. CONCLUSIONS: HIV infection induces substantial changes in the immune profile of the female genital tract. Further study of the implications of these findings for HIV acquisition and transmission is needed.

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## 6. EPIDEMIOLOGY

### "Nearly half of Indian women have not heard of AIDS"

**Date:** 23 February 2007

**Source:** *Reuters*

**Author(s):** Kamil Zaheer

[http://news.yahoo.com/s/nm/20070223/india\\_nm/india288936](http://news.yahoo.com/s/nm/20070223/india_nm/india288936)

More than 40 percent of women in India have not heard of AIDS, according to a government survey that has alarmed activists.

India has 5.7 million people living with HIV/AIDS, according to the United Nations, which is the world's highest caseload. But the prevalence rate, in the country of 1.1 billion people, is much lower than in most of Africa.

The National Family Health Survey (NFHS), the most extensive study on health and nutrition in India, said in its latest report only 57 percent of women have heard of AIDS. In rural areas, where most Indians live, less than half the women -- 46 percent -- were aware of the disease.

Activists said on Friday that poor awareness among women was fuelling the epidemic. "This shows women don't have access to information, translating into more women getting infected," said Anjali Gopalan, head of Naz Foundation India, a leading anti-AIDS group.

In the past few years, there has been a growing "feminisation" of the epidemic in India with nearly 40 percent of all those infected now being women, including housewives. "Biologically, women are more susceptible to HIV," said Christy Abraham of ActionAid-India. "The lack of awareness adds to the HIV threat they face."

One reason for low awareness is that the government has focused prevention efforts on high-risk groups like prostitutes and intravenous drug users, rather than on the general population. "But we are expanding prevention efforts among the general population in rural areas, especially women, over the next five years," a government official said on condition of anonymity.

Many rural women have been infected by their husbands who work in the cities and visit prostitutes. Stigma stops infected husbands from telling their wives they are HIV-positive.

The NFHS survey, supported by UNICEF as well as the British and U.S. governments, shows a gulf in awareness between men and women, with 80 percent of men having heard of the disease. Only 54 percent of Indian women are literate compared with 76 percent for men. Many women in villages do not have television in their homes and miss out on anti-AIDS advertisements, say activists, calling for a broad-based effort to educate and empower women. "Even if they do have TVs, there is no electricity in many areas. This is one way how fighting HIV is linked to the issue of general development," Abraham said.

Activists want the government to spend more training and sending grassroots health workers to spread AIDS education among women, especially in poorer and highly populated states. In Bihar -- home to 85 million people -- only 35 percent of women have heard of AIDS, with the level of awareness falling to 30 percent in villages.

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## 7. OTHER PREVENTION APPROACHES

### "Speeding HIV's deadly spread"

**Date:** 02 March 2007

**Source:** *Washington Post*

**Author(s):** Craig Timberg

<http://www.washingtonpost.com/wp-dyn/content/article/2007/03/01/AR2007030101607.html>

The young and hip at ground zero of the AIDS epidemic meet, drink and pair off under the knowing gaze of bartender Brian Khumalo. Sometimes they first buy a three-pack of condoms from the box he keeps by the liquor, sometimes not.

Night after night they return for the carefree, beery vibe, with the same partners or new ones, creating a web of sexual interaction. A growing number of studies single out such behavior -- in which men and women maintain two or more ongoing relationships -- as the most powerful force propelling a killer disease through a vulnerable continent.

This new understanding of how the AIDS virus attacks individuals and their societies helps explain why the disease has devastated southern Africa while sparing other places. It also suggests how the region's AIDS programs, which have struggled to prevent new infections even as treatment for the disease has become more widely available, might save far more lives: by discouraging sexual networks.

"The problem of multiple partners who do not practice safe sex is obviously the biggest driver of HIV in the world," said Ndwapi Ndwapi, a top government AIDS official in Botswana, speaking in Gaborone, the capital. "What I need to know from the scientific community is, what do you do? . . . How do you change that for a society that happens to have higher rates of multiple sexual partners?"

Khumalo, 25, tall and lanky with a crooked-toothed smile, described the problem succinctly as he pointed to a spiky-haired woman in a corner booth of the bar. "She's new around here, so every guy is going to talk to her," he said. "She will be with me today. Tomorrow she will be with my best friend. And I will be with somebody else."

Khumalo moved from Gaborone to Francistown last March, finding a city of 85,000 with a red-brick downtown, modest concrete homes and an accommodating sexual culture. The first night, he slept with a woman he had just met, he said. He did the same the second night, the third, the fourth.

Though he used condoms each time, he said, an alarmed friend soon drove him to the white, low-slung buildings of Francistown's biggest AIDS clinic. "I saw thousands of beautiful women going to get pills," Khumalo recalled.

It scared him, but not enough. By the end of the year, Khumalo had slept with more than 100 women, he said.

But the number of sexual partners is not the only factor that increases the risk of AIDS. The most potentially dangerous relationships, researchers say, involve men and women who maintain more than one regular partner for months or years. In these relationships, more intimate, trusting and long-lasting than casual sex, most couples eventually stop using condoms, studies show, allowing easy infiltration by HIV.

Researchers increasingly agree that curbing such behavior is key to slowing the spread of AIDS in Africa. In a July report, southern African AIDS experts and officials listed "reducing multiple and concurrent partnerships" as their first priority for preventing the spread of HIV in a region where nearly 15 million people are estimated to carry the virus -- 38 percent of the world's total.

But for many Botswana, as citizens of this landlocked desert country of 1.6 million call themselves, it is a strategy that has rarely been taught.

"There has never been equal emphasis on 'Don't have many partners,' " said Serara Selelo-Mogwe, a public health expert and retired nursing professor at the University of Botswana, who recalled stepping past broken bottles and used condoms as she arrived on campus each Monday morning. "If you just say, 'Use the condom' . . . we will never see the daylight of the virus leaving us."

#### *A Lethal Mix of Causes*

International experts long regarded Botswana as a case study in how to combat AIDS. It had few of the intractable social problems thought to predispose a country to the disease, such as conflict, abject poverty and poor medical care. And for the past decade, the country has rigorously followed strategies that Western experts said would slow AIDS.

With its diamond wealth and the largess of international donors, Botswana aggressively promoted condom use while building Africa's best network of HIV testing centers and its most extensive system for distributing the antiretroviral drugs that dramatically prolong and improve the lives of those with AIDS.

But even though the relentless pace of funerals began to ease in recent years, the disease was far from under control. The national death rate fell from the highest in the world, but only to second-highest, behind AIDS-ravaged Swaziland. Men and women in Botswana continued to contract HIV faster than almost anywhere else on Earth.

Twenty-five percent of Botswana adults carry the virus, according to a 2004 national study, and among women in their early 30s living in Francistown, the rate is 69 percent.

Researchers increasingly attribute the resilience of HIV in Botswana -- and in southern Africa generally -- to the high incidence of multiple sexual relationships. Europeans and Americans often have more partners over their lives, studies show, but sub-Saharan Africans average more at the same time.

Nearly one in three sexually active men in Botswana reported having multiple, concurrent sex partners, as did 14 percent of women, in a 2003 survey paid for by the U.S. government. Among men younger than 25, the rate was 44 percent.

The distinction between having several partners in a year and several in a month is crucial because those newly infected with HIV experience an initial surge in viral loads that makes them far more contagious than they will be for years. During the three-week spike -- which ends before standard tests can even detect HIV -- the virus explodes through networks of unprotected sex.

This insight explained what studies were documenting: Africans with multiple, concurrent sex partners were more likely to contract HIV, and countries where such partnerships were common had wider and more lethal epidemics.

A model of multiple sexual relationships presented at a Princeton University conference in May showed that a small increase in the average number of concurrent sexual partners -- from 1.68 to 1.86 -- had profound effects, connecting sexual networks into a single, massive tangle that, when plotted out, resembles the transportation system of a major city.

A second key factor helping the virus spread through southern Africa is low rates of circumcision. Before European colonialists arrived, most tribes in the region removed the foreskins of teenage boys during manhood rituals. Those rites, which were discouraged by missionaries and other Westerners who regarded them as primitive, have gradually declined as the region rapidly modernized.

Dozens of studies, including three experimental trials conducted in Africa in recent years, show that circumcised men are much less likely to contract HIV because the most easily infected cells have been removed.

These factors, researchers say, explain how North Africa, where Muslim societies require circumcision and strongly discourage sex outside monogamous and polygamous marriages, has largely avoided AIDS. They also explain why the epidemic is far more severe south of the Sahara, where webs of multiple sex partners are more common, researchers say.

West Africa has been partially protected by its high rates of circumcision, but in southern and eastern Africa -- which have both low rates of circumcision and high rates of multiple sex partners -- the AIDS epidemic became the most deadly in the world.

"That's the lethal cocktail," said Harvard University epidemiologist Daniel Halperin, a former AIDS prevention adviser in Africa for the U.S. government, speaking from suburban Boston. "There's no place in the world where you have very high HIV and you don't have those two factors."

### *No Word for 'Fidelity'*

From under the broad thatched roof of Francistown's Customary Court, which handles minor crimes and misconduct, Chief Judge Ludo Margaret Mosojane had long suspected that the city's torrent of AIDS deaths flowed from its sexual culture. Each year brought more cases resulting from elaborate, overlapping relationships, she said.

"It explains why Africa is hardest hit" by AIDS, Mosojane said. "The way we contract for sex is different from how others do it."

Polygamy once was common in the region, and in some parts still is; Swaziland's king has 13 wives. In generations past, even Botswana with just one spouse rarely expected monogamy. Husbands spent months herding cattle while their wives, staying elsewhere, tended crops, Mosojane said. On his return, a husband was not to be quizzed about his activities while he was away. He also was supposed to spend his first night back in an uncle's house, giving his wife time to send off boyfriends.

In Setswana, the national language, "the word 'fidelity' does not even exist," Mosojane said.

The few checks that traditional villages had on sexual behavior dwindled during the development frenzy after 1967, when diamonds were discovered. Botswana increasingly moved to cities for school or work. Plentiful television sets delivered a flood of Western images, including racy soap operas and music videos featuring lightly clad women vying for the attention of wealthy, bejeweled men.

Francistown, with nearby mines, military camps and border posts overflowing with desperate refugees, changed faster than most cities. Amid the bustling malls, there was soon an unsettling concentration of young adults because so many people ages 35 to 50 had already died of AIDS complications, residents say.

Faruk Maunge, 36, a high school counselor whose dreadlocks, goatee and rectangular glasses give him a cosmopolitan air, noticed the changes when he returned from stays abroad. "They are just a lost bunch," he said. "They are very, very reckless."

Maunge said that rent, clothing, even cellphone airtime became part of implicit sexual exchanges. Men and women maintained two, three, even four regular partners. The toll was clear from the snapshots he kept in a green plastic first-aid box.

"This one is gone," Maunge said, pointing to a faded picture of a woman in a red top who was nibbling her fingernails. Moving deeper into the pile, he continued: "This one is gone, Mooketsi. And this one is gone, Themba. This one is gone, too, this one on the far left. This one is positive."

With a hint of frustration, Maunge said of one man, "He's sleeping around again." Maunge also grew irritated at a picture showing a friend with AIDS who seemed to father a child -- he was awaiting his fourth -- with every girlfriend.

Maunge said he once was reckless, too, having sex with three women in a week, sometimes without condoms. But after watching the disease kill more than 20 of his friends, he settled down with a new girlfriend and stayed faithful, he

said.

"Praise God, I've been lucky," Maunge said. "It's like you have 10 bullets going through you and none hits you."

### *The Missing Message*

On a hospital wall here, not far from the AIDS clinic that Khumalo visited with his friend, the painted image of a condom shimmers like a comic-book superhero. Giant, colorful block letters declare, "CONDOMISE AND STAY ALIVE!!"

In cramped black script below, it adds, "Abstain first."

Yet rarely seen among Botswana's AIDS prevention messages is one that has worked in other African countries: Multiple sex partners kill. Dubbed "Zero Grazing" by Ugandan President Yoweri Museveni, this approach dominated in East Africa, where several countries curbed HIV rates.

Fidelity campaigns never caught on in Botswana. Instead, the country focused on remedies favored by Western AIDS experts schooled in the epidemics of America's gay community or Thailand's brothels, where condom use became so routine it slowed the spread of HIV.

These experts brought not just ideas but money, and soon billboards in Botswana touted condoms. Schoolchildren sang about them. Cadres of young women demonstrated how to roll them on. The anti-AIDS partnership between the Bill & Melinda Gates Foundation and drugmaker Merck budgeted \$13.5 million for condom promotion -- 25 times the amount dedicated to curbing dangerous sexual behavior.

But soaring rates of condom use have not brought down high HIV rates. Instead, they rose together, until both were among the highest in Africa.

The focus on condoms endured even after the arrival of internationally heralded "ABC" programs, named for their prescription of "Abstain, Be Faithful and Condomize." The middle concept -- fidelity -- often got lost.

The few posters advocating it in Francistown are old and torn; ads for condoms and abstinence are far more prominent. A 2004 government study measured the result: Three-quarters of Botswana surveyed knew that condoms could stop the spread of HIV. Half knew that abstinence would. Yet only one in five knew that fidelity to a single, uninfected partner prevented spreading the disease.

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## **8. POLITICS AND POLICY**

### **"Biomedical research faces flat budget for 2008"**

**Date:** 28 February 2007

**Source:** *Nature Medicine*

**Author(s):** Alan Dove

With the US government's 2007 budget still in limbo, the Bush administration released its proposed 2008 budget on 5 February - and the news for biomedical research is universally bad. The administration claims to boost funding for the US National Institutes of Health (NIH) by \$232 million in the 2008 proposal, but a closer look at the latest 2007 budget numbers reveals that the institute will effectively get a \$500 million cut, even before accounting for inflation.

Worse, more than 10,000 NIH extramural grants, which usually run three to four years, are up for renewal in 2008, the biggest crop of renewals since budget declines began four years ago. That means an unusually large number of investigators will be competing for an unusually small pool of money. "Certainly the biomedical research community has to be disappointed with the NIH budget that has declined in real terms since 2004," says Kei Koizumi, director of the budget and policy program at the American Association for the Advancement of Science (AAAS).

With fewer than 18% of NIH extramural grants receiving funding and the average age of first-time grant winners topping 40, the future may be especially tough for young investigators (*Nat. Med.* 12, 1224; 2006). "Senior research investigators who've had funding for 20 to 25 years are having to shut down their labs [and] young people are shunning biomedical research careers," says Leo Furcht, president of the Federation of American Societies for Experimental Biology.

For 2008, even the popular tactic of linking one's research to biodefense may fail. According to a AAAS analysis, the NIH biodefense budget, administered primarily by the US National Institute of Allergy and Infectious Disease, faces a 0.7% cut.

In 2006, the Bush administration approved minuscule increases or even cuts for funding of biomedical research. As *Nature Medicine* goes to press, however, the newly Democratic Congress is debating a bill that would rescue the 2007 NIH budget from the proposed \$28.6 billion, bumping it up to \$29.1 billion. If that bill passes, the president's \$28.8 billion proposal for NIH in 2008 would in effect be a cut from the 2007 levels. Counting a required payment to the Global Fund to Fight AIDS, Tuberculosis and Malaria, the institutes stand to lose \$529 million in 2008.

With inflation, the NIH has lost about 12% of its total purchasing power since 2004, when a campaign to double the agency's budget ended. The nosedive the NIH has taken since then makes many observers question a new scheme to double the budget of the US National Science Foundation. The NIH cuts are in part funding that increase. "While we applaud the efforts to shore up agencies who have not had as much attention in the recent past," says Furcht, "we would submit that it should not come at the expense of the NIH."

### **"Judge: US can deny federal funding to AIDS groups that don't disavow sex trafficking"**

**Date:** 27 February 2007

**Source:** *Associated Press*

<http://www.iht.com/articles/ap/2007/02/28/america/NA-GEN-US-AIDS-Funding.php>

A federal appeals court ruled that the Bush administration can deny funding to nonprofit AIDS groups that do not publicly disavow prostitution and sex trafficking. Overturning a lower court's decision, the U.S. Court of Appeals for the District of Columbia said Tuesday that the AIDS groups' free speech rights would not be violated if the money was linked to a pledge to uphold government policy.

At issue is the case of DKT International Inc., which provides family planning and HIV/AIDS prevention programs in 11 countries. The group, which helps distribute condoms to prostitutes and other sex workers in Vietnam, has refused to sign a pledge to support the Bush administration policies. In 2005, DKT sued the U.S. Agency for International Development, contending its free speech rights were violated by a 2003 law requiring groups to explicitly oppose prostitution and sex trafficking in order to qualify for part of a \$15 billion (€11.34 billion) AIDS program. A U.S. District Court ruling last year agreed, saying the funding conditions insist that groups "parrot" the U.S. government's position on prostitution. But U.S. Circuit Judge A. Raymond Randolph said Congress has authorized the Bush administration to assist non-governmental organizations like DKT "on such terms and conditions as the president may determine."

"The act does not compel DKT to advocate the government's position on prostitution and sex trafficking; it requires only that if DKT wishes to receive funds it must communicate the message the government chooses to fund," Randolph wrote in a 10-page decision reversing the lower court's ruling. "This does not violate the First Amendment."

Calls for comment to DKT's offices in Washington were not immediately returned Tuesday.

### **"Women's health office funds cut"**

**Date:** 27 February 2007

**Source:** *Washington Post*

**Author(s):** Rick Weiss

<http://www.washingtonpost.com/wp-dyn/content/article/2007/02/26/AR2007022601584.html>

When is \$4 million really \$2.8 million? One answer is "When you're a woman," as the Labor Department has repeatedly found that women earn about 75 cents for every dollar that men earn for the same work.

But this week's answer is "When you are the Office of Women's Health" within the Food and Drug Administration. That office, which was at the center of a politically damaging storm over the emergency contraceptive "Plan B," just had more than one-quarter of this year's \$4 million operating budget quietly removed, insiders say. The office funds research on male-female biological differences to ensure that women receive the most appropriate drug doses and treatments. It also produces heavily requested health information about menopause, pregnancy, birth control, osteoporosis and other topics.

The administration had requested -- and Congress had budgeted -- \$4 million for the office in fiscal 2007, just as they have for several years running. Last week, however, word came down that the FDA intends to withhold \$1.2 million of that, apparently for use elsewhere in the agency. Because the remaining \$2.8 million has already been spent or allocated for salaries and started projects, the office must effectively halt further operations for the rest of the year, according to a high-level agency official with knowledge of the budget plan, who spoke on the condition of anonymity because the official is not authorized to speak publicly.

FDA spokesman Robert Ali said in an e-mail that, as a matter of policy, the agency does not discuss its spending plan until Congress has had a chance to review it and comment. However, he added, "the spending plan for the agency is to allow our operating components to spend at least at their 06 level" -- in other words, the full \$4 million. But FDA

spokeswoman Julie Zawisza quickly corrected that statement in a follow-up e-mail, saying the spending plan for the agency is "INTENDED" to allow spending of at least the 2006 level, acknowledging that the spending plan is not ironclad.

Women's health advocates inside and outside the agency suspect they are witnessing, at least in part, a long-anticipated payback for the trouble the office stirred during the prolonged debate over nonprescription sales of Plan B. Taking a position that chafed the administration's conservative base, the office had stood up for scientific research that had backed the safety and appropriateness of such sales. In 2005, the office's then-director, Susan Wood, resigned in protest over the issue, a major embarrassment to the agency. A compromise was finally reached last August that allowed over-the-counter sales of the drug to people at least 18 years old.

Martha R. Nolan, a vice president at the Society for Women's Health Research, a Washington advocacy group, said that big budget bites in Washington are often the beginning of the end and that she worries that this is retribution for the Plan B controversy. "We fear this is the first step toward eliminating the Office of Women's Health," Nolan said. "We must not allow this office to be eliminated or reduced to an empty shell that has no program funding."

The office was created in 1994 amid growing evidence that some sex-based differences in biology warranted special regulatory attention -- and a recognition that other offices within the FDA did not have the time, money or expertise to focus on women's special needs. More than 200 research articles based on studies funded by the office have appeared in scientific journals since 1994, and the office's fact sheets and other publications have generated record-breaking responses in recent years.

FDA Commissioner Andrew C. von Eschenbach is to appear today before the Senate appropriations subcommittee to discuss the agency's 2008 budget. Tomorrow, he will have a repeat performance before the House.

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## 9. PHARMACEUTICAL INDUSTRY

### "Clinical trials in India just got cheaper"

**Date:** 28 February 2007

**Source:** *Drug Researcher.com*

**Author(s):** Kirsty Barnes

<http://drugresearcher.com/news/ng.asp?id=74588>

India's budget finance minister has today announced a tax exemption on all services carried out by its contract research and clinical trials industry - a saving of 12.24 per cent. The exemption proposal has been already approved by parliament and will come into effect at the start of India's financial year on 1 April 2007.

The decision removes a previous stumbling block that international pharmaceutical sponsors faced when considering contract research organisations (CROs) in India and is designed to give a boost to this budding market. "This is very positive news for India's contract research industry and will definitely have an impact in the decision making process for many pharmaceutical companies," Dr Umakanta Sahoo, managing director of Chiltern International in India told

Outsourcing-Pharma.com. "This saving of 12.24 per cent is a big amount - a saving that will now be passed onto clients."

Cost-savings are a significant draw card for many pharmaceutical companies when deciding to outsource clinical research to countries in emerging markets such as India and Latin America. In the last 10 years, skyrocketing costs of R&D have led to a growth explosion in the clinical services industry as pharma companies scramble to cut costs. The average cost of running a US-based clinical trial per patient is \$5,404 for Phase I, \$6,538 for Phase II and \$7,635 for Phase III. According to an analysis last year by Rabo India Finance, conducting a clinical trial in a lower-cost destination such as India, for example, can cost up to 60 per cent less than in the US.

However, while quickly gaining momentum, India's much hyped clinical research industry is still yet to really take off. Since its introduction of patent protection laws in 2005, the industry has been growing three digits, however, this growth has not been as fast as many have predicted. A report by analysts at McKinsey estimated that clinical research in India will be a \$1bn (€800,000m) industry by 2010, although many analysts expect it will be closer to half that. It is hoped that this move by the Indian government will give the industry the kick that it needs to live up to expectations. "To make India a preferred destination for drug testing, I propose to exempt clinical trial of new drugs from service tax," says an extract from article 157 of the Government of India's Budget for the year 2007-08.

"Also, total exemption from service tax is being provided to technical testing and analysis for testing of new drugs, vaccines and herbal remedies, on human participants by a CRO approved to conduct clinical trials by the Drugs Controller General of India."

"This exemption from Government of India will attract more clinical trial outsourcing as the pharmaceutical sponsors will heavily benefit on their cash outflows on account of their expenses on CRO fees and other variable pass through expenses," said India's budget finance minister Palaniappan Chidambaram.

The contract research industry in India is only beginning to sprout its wings and until now there has been much domestic debate as to whether this sector should be subject to the same service tax that other industries in the country face. In the 2005-06 budget, CROs were required to pay 10 per cent service tax. In the 2006-07 budget, this tax was raised to the current level of 12.24 per cent, which is much higher than similar service taxes of around 4 per cent in other countries such as the UK.

Currently, CROs are having to ask sponsors for reimbursement of this service tax and paying it to the government. Hence today's announcement comes as a welcome surprise to the contract research industry, which has been heavily petitioning the government for the exemption in a boost international business. "The Scientific Committee and the Ministry of Health in India have both been very supportive of this decision and this sends out very positive signals to international firms that India is taking the continued development of this industry very seriously," said Sahoo.

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