



# ALLIANCE FOR MICROBICIDE DEVELOPMENT

01 June 2007, Volume 8, Number 21

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 complete issues of the *Digest* or search by keyword for individual articles at <http://www.microbicide.org/publications/>. If you would like to be removed from the *Digest* distribution list, please send an email to [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

### June 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 Stephanie Tillman, Alliance Writer/Research Associate, by email ([stillman@microbicide.org](mailto:stillman@microbicide.org)) or by phone (301-587-3302) with any updates, questions, or comments.

<i>Candidate</i>	<i>Mechanism of Action</i>	<i>Developer</i>	<i>Phase*</i>
ACIDFORM (Amphora)	Vaginal defense enhancer	CONRAD; Instead, Inc.	3**
BufferGel	Vaginal defense enhancer	ReProtect, Inc.	2/2B
Carraguard	Entry/fusion inhibitor	Population Council	3

Dapivirine (TMC120)	Replication inhibitor	IPM	1/2
Invisible Condom	Entry/fusion inhibitor	Laval University	1/2
PC 815	Combination	Population Council	1
Praneem	Uncharacterized mechanism	Talwar Research Foundation	2
PRO 2000	Entry/fusion inhibitor	Indevus Pharmaceuticals	3
Tenofovir (PMPA gel)	Replication inhibitor	CONRAD	2B
UC-781	Replication inhibitor	CONRAD	1
VivaGel (SPL7013)	Entry/fusion inhibitor	Starpharma Ltd.	1

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For modifications, please contact Stephanie Tillman, email [stillman@microbicide.org](mailto:stillman@microbicide.org), tel. 301-587-3302.

\*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.

\*\*The Phase 3 trial of ACIDFORM will evaluate the effectiveness of the diaphragm with ACIDFORM gel in preventing acquisition of *N. gonorrhoeae* and/or *C. trachomatis*. It is not intended to assess effectiveness for HIV prevention.

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## 2. MEDIA COVERAGE OF MICROBICIDES

### "Getting the health care we need instead of the products someone wants to sell"

**Date:** 31 May 2007

**Source:** *Womens Health Activist*

**Author(s):** Executive Director's Column

[http://www.nwhn.org/wha\\_mayjune07\\_ed](http://www.nwhn.org/wha_mayjune07_ed)

Reading the articles in this issue has made me think a lot about how often our health care becomes distorted away from its essential purpose - to care and to support health. Instead, our visits with health care providers and our awareness of health issues are heavily influenced by the marketing of profitable products. Take statins, for example. These cholesterol-lowering drugs are among the heavily used medications in the U.S. It's hard to watch TV without seeing an advertisement for one of the many statins on the market. The ads imply high cholesterol alone is enough to make taking a statin worthwhile, and that men and women benefit equally. Not so! In her article, Electra Kaczorowski explains what studies have and haven't shown about the effectiveness of statins in women and concludes that a focus on health would lead to a dramatically different approach to preventing heart disease

The new HPV vaccine is another example of marketing going way beyond the real need for the product. Alicia Bell's

article on does a great job explaining what the HPV vaccine can and can't do to improve the health of young women and reduce the likelihood of developing cancer. A slow and sensible approach to introducing this vaccine in the U.S. would make sense for many reasons, but that's not what's happening. Instead, the manufacturer of this vaccine is pushing hard for millions of young women to get the shot in the next few months, as part of school vaccination programs. Why the rush? It seems pretty obvious to us that the manufacturer wants to corner the market before another vaccine is approved. In fact, the FDA is reviewing another HPV vaccine right now.

The fact that we don't yet have a safe and effective **microbicide** for women to use to protect themselves against HIV and other sexually transmitted infections is another painful example of how the development of products we need takes a back seat to companies' focus on products with a large profit margin. Bindiya Patel's cover story about **microbicides** explains how dedicated researchers working in respectful collaboration with activists can come up with exciting new products and ethical approaches to testing them in women. But, and this is a very big but, it's 20 years after women started talking about the need for a **microbicide**, and we still don't one. Funding for **microbicide** research has come mostly from the government and private foundations - and it hasn't been nearly enough. The pharmaceutical industry could have seen this need, thrown their resources into the problem and gotten products to market years ago. But most big pharmaceutical companies believe that the market for HIV protection won't be profitable, and have been slow to act in this field.

**EDITORS' NOTE: The above-referenced article written by Bindiya Patel is included in this issue of the News Digest in the category, "Media Coverage of Microbicides."**

As we raise women's voices for health care for all, let's keep talking about what health means to us, and what we really need, and keep working to make that a reality for all women!

### **"Setbacks and steps forward in the search for safe and effective microbicides"**

**Date:** 31 May 2007

**Source:** *Womens Health Activist*

**Author(s):** Bindiya Gillenwater Patel

[http://www.nwhn.org/wha\\_mayjune07\\_microbicides](http://www.nwhn.org/wha_mayjune07_microbicides)

Worldwide, women are disproportionately impacted by the HIV/AIDS epidemic. More women are newly infected with HIV than men, primarily through having sex with men who are HIV-positive.[1] In the U.S., more than 250,000 women are living with HIV/AIDS, and the disease is the number one cause of death among African American women aged 25-34.[1,2] And, internationally, around half of the 38.6 million people living with HIV are women.[3] For this reason, advocates around the world have long voiced the need for an HIV prevention method that women can control.

**Microbicides** - products that are designed to be used in a gel, tablet, or vaginal ring to help prevent HIV/AIDS - could provide exactly that. Due to advocates' work around the world, and the recent attention on **microbicides** at the 2006 International AIDS Conference in Toronto, millions of people have heard about **microbicides**. The challenge the field now faces is to find the correct balance between building enthusiasm and political support for **microbicides**, while

avoiding raising unrealistic expectations in the media or in our outreach work.

**Microbicides** are not going to be a magic bullet against HIV. It is important to note that, while **microbicides** will help people reduce risk of infection, they will never be as effective as condoms. We still need to improve people's access to the interventions that we know work now: making sure that male and female condoms are available and affordable; ensuring that pregnant women get access to services that prevent maternal transmission to their babies; and promoting appropriate male circumcision programs.

Nonetheless, **microbicides** have the potential to be an important way for women and couples to reduce their risk of infection. The hope is that couples will be able to use **microbicides** more consistently than they currently do condoms. We need to encourage people to continue to use condoms if they possibly can, and suggest additional use of **microbicides** for back-up protection and added pleasure.

#### *Timing for **Microbicide** Availability*

Although **microbicides** do not yet exist, ten products are currently being tested in clinical trials, and anticipation is building: results from the first **microbicide** effectiveness trials could be available in 2008. (See chart at [http://www.nwhn.org/wha\\_mayjune07\\_microbicides](http://www.nwhn.org/wha_mayjune07_microbicides) for products undergoing large scale human effectiveness trials). Then it will take at least one or two years for the products to be reviewed and approved. Thus, while a **microbicide** could be ready for introduction by 2010, it's likely only to happen in a few countries, most likely through smaller scale, introductory programs. If the products currently in effectiveness trials do prove effective, the timeline will be longer. There are several second-generation leads already in human testing, and we need to ensure that the entire pipeline of products advances.

In January, 2007, however, the search for an effective **microbicide** faced a major setback when the trials of one potential product were stopped due to safety concerns. Shortly thereafter, in March 2007, the U.S. House of Representatives and Senate both introduced legislation to provide a much-needed boost to the **microbicides** field. We'll discuss both of these developments below.

#### *Cellulose Sulfate Trials Close Due to Safety Concerns*

In order to fully understand the recent **microbicide** trial closures, a bit of background information on clinical trials is useful. Before any new drug is available to consumers, it goes through a series of rigorous series of clinical tests in people. The first two levels of these safety tests, called Phase I and Phase II trials, look for evidence that the product could be harmful. If a product gets through Phase I and II safety trials without evidence that it might cause harm, it can then move to Phase III effectiveness trials, which compares the new product to a standard product or a placebo. The **microbicide** gel cellulose sulfate (CS) went through two Phase I and II trials, without results to indicate that it was harmful. CS proceeded to Phase III trials, in which one group of women used the experimental gel (CS), while another group of women used a placebo gel without the active ingredient.

Extensive measures are taken to help all **microbicide** trial participants understand that they should not count on the gel for protection from HIV, that half would receive the placebo gel, and that they have the right to withdraw from the trial at any time. All participants receive monthly HIV prevention counseling, free condoms, and prompt diagnosis and treatment for any sexually transmitted infections. Finally, an independent Data Safety Monitoring Board (DSMB) exists

for each **microbicide** trial. The DSMB is composed of individuals with expertise in statistics, medicine, clinical trials, and community issues; it serves to protect participant safety and recommends whether a particular trial should continue.

Cellulose sulfate was one of four **microbicides** in Phase 3 effectiveness trials for HIV/STI prevention (the other three are BufferGel, Carraguard, and PRO2000). CONRAD was conducting Phase III trials to assess CS' effectiveness in Benin, India, South Africa, and Uganda. A similar trial, sponsored by Family Health International (FHI), was also underway in Nigeria. Both sponsors are U.S.-based nonprofit research groups dedicated to advancing health in developing countries. In January, at the recommendation of their respective DSMBs, both groups discontinued their CS trials after CONRAD's DSMB found evidence suggesting that the **microbicide** might be contributing to an increased risk of HIV infection. (In other words, more HIV infections occurred in women using the experimental gel than among women using the placebo.) Although review of the data from the Nigerian trial found no evidence of increased risk, FHI felt that the only responsible course of action was to halt its study also. Interim results of the other three ongoing Phase 3 trials have been reviewed by their respective DSMBs, which have found no evidence of similar safety concerns.

Once their trials closed, the FHI and CONRAD investigators quickly shifted their efforts to notifying the trial participants, collecting any un-used gels, and ensuring that participants received appropriate follow-up care - including counseling, HIV testing, and medical referrals, if needed. In response to demands from advocates, many trial sponsors now develop written agreements before trials begin. In this case, both trial sponsors had prepared written agreements in advance with local providers to assure that any women infected while enrolled in the trial would get ongoing care and treatment.

In the days following the closure of the CS trial, women from around the world voiced a strong demand for information about what went wrong with these trials and support for continuing the search for a safe, effective **microbicide**. Women still don't have the tools they need to protect themselves from HIV. The Global Campaign for **Microbicides** and the African **Microbicide** Advocacy Group are continuing to answer advocates' questions; facilitate dialogue and debate; and develop an advocacy agenda that prioritizes participants' rights, enhances scientific transparency, and encourages deep scientific reflection.

#### *Demonstrating Public Demand in the U.S. - the **Microbicide** Development Act*

In the wake of the CS trials' closure, advocates, researchers and legislators are working together to ensure sufficient public funding for the continued search for a safe and effective **microbicides**. Since the pharmaceutical industry has not yet invested significantly in this field, **microbicide** research depends on governmental and philanthropic investment. Yet, right now, barely three percent of the U.S. budget for HIV/AIDS research is spent on developing **microbicides**.

To mark International Women's Day on March 8, 2007, a bipartisan group of senators and representatives introduced the **Microbicide Development Act (MDA) of 2007**. Sponsors include Sen. Barack Obama (D-IL), Sen. Olympia Snowe (R-ME), Rep. Jan Schakowsky (D-IL), and Rep. Christopher Shays (R-CT). The Act calls for improved coordination and expanded resources for **microbicide** research and development activities at the National Institutes of Health, the Center for Disease Control, and the U.S. Agency for International Development. NWHN members can

play a pivotal role by contacting your legislators to support the MDA. A petition, sample letter, and advocacy email system are available here. If you call your Congress members, give them this simple message: "I am calling to ask Representative/Senator \_\_\_\_\_ to sponsor the H.R.1420 / S.823 **Microbicide Development Act**. This bill can really make a difference in addressing the AIDS pandemic by supporting the development of important HIV prevention options that women can control."

The real heroines and heroes are the women who enroll in these trials. Over two years, on average, trial participants each attend 29 study visits - including monthly visits for HIV and pregnancy tests - and go through 11 pelvic exams. Without their participation and commitment, it would be impossible to discover an effective **microbicide**. This month, take a moment to write or call your legislators to honor their commitment and move one step closer to getting a new prevention tool into women's hands.

#### REFERENCES

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3. Joint United Nation Programme on HIV/AIDS (UNAIDS). Report on the Global AIDS Epidemic: 2006, Geneva: World Health Organization. 2006. pp. 8, 45-46.

*Bindiya Patel is Special Projects Manager for the Global Campaign for **Microbicides**, and a proud board member for the National Women's Health Network.*

#### "Advances in AIDS crisis but more to be done"

**Date:** 29 May 2007

**Source:** *Canberra Times*

**Author(s):** Anthony S. Fauci

[http://canberra.yourguide.com.au/detail.asp?class=your%20say&subclass=general&story\\_id=589728&category=Opinion](http://canberra.yourguide.com.au/detail.asp?class=your%20say&subclass=general&story_id=589728&category=Opinion)

It is now a quarter of a century since the acquired immune deficiency syndrome was recognised. The knowledge that has been gained since then has been breathtaking, and the pace at which basic research has been translated into lifesaving treatments is unprecedented.

The discovery of the human immunodeficiency virus as the cause of AIDS was followed by elucidation of its pathogenesis, natural history, and epidemiology, the creation of a diagnostic blood test, and the development of antiretroviral drugs. In 1996, the approval of the first drug of a class called protease inhibitors led to the adoption of a multi-drug, anti-HIV regimen known as highly active antiretroviral therapy, or HAART. This advance dramatically transformed the quality of life and extended the life expectancy of HIV-infected individuals.

Moreover, antiretroviral drugs given to pregnant HIV-infected women and newborns have proven enormously successful in preventing mother-to-child transmission of HIV. As a result, since these combinations of drugs were introduced, at least three million years of life have been saved in the United States alone. We now have more than two dozen approved anti-HIV drugs and drug combinations, and a robust pipeline of next-generation drugs in various stages of development and clinical testing.

But nowadays our task is to apply these scientific and technological advances to delivering treatment and prevention strategies to people throughout the world, particularly those in resource-poor nations. Despite the successes in treating HIV/AIDS in the US and other developed countries, it is clear that efforts to combat the pandemic must be scaled up in Africa, Asia, and other parts of the world where HIV/AIDS exacts its greatest toll. Indeed, an estimated 40 million people throughout the world are infected with HIV; nearly three million died of AIDS in 2006 alone.

Programs such as the President's Emergency Plan for AIDS Relief, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and philanthropies like the Bill and Melinda Gates Foundation and the Clinton Foundation have helped make drugs available to treat two million people infected with HIV in lower- and middle-income countries. But fewer than 25 per cent of the people in these countries who need antiretroviral drugs are receiving them.

With 4.3 million new HIV infections each year throughout the world, new HIV infections far outstrip our ability to treat all those infected. Improvements in our ability to prevent HIV infections from occurring are desperately needed.

A wide array of prevention strategies, including behavioral modification, distribution of condoms, and the provision of clean needles and syringes to intravenous drug users, has emerged. Recent studies suggest that adult male circumcision can be a promising prevention strategy, if properly and hygienically performed, and accompanied by appropriate counselling and post-surgical care. Likewise, the ongoing development of topical **microbicides** offers the hope of empowering women to protect themselves from HIV infection when using condoms or refusing sexual intercourse is not feasible.

But the greatest scientific and public health goal in HIV/AIDS research still eludes us: the development of an effective HIV vaccine. This challenge has been particularly difficult because of the nature of the virus, particularly its ability to integrate itself into the genome of host cells, to readily mutate, and to conceal that part of its outer coat that would induce protective antibodies.

We also know the body's natural immune response against HIV is inadequate in containing or controlling the virus. Indeed, since the discovery of HIV, there has never been a documented case in which an individual's immune system has eradicated the virus following established infection.

Many current studies focus on developing vaccines that might not completely prevent HIV infection, but could slow the progression of HIV or make a person less likely to pass the virus on to others. But our ultimate goal is to develop a vaccine. To succeed, we must solve the mystery of how to induce the human body to produce a protective immune response.

Despite the extraordinary scientific and medical accomplishments in the battle against HIV/AIDS so far, history will

judge us by what we accomplish in the next quarter-century, and how we respond to the challenge of delivering the fruits of our research efforts to those who need them most.

*Anthony Fauci is director of the US National Institute of Allergy and Infectious Diseases and adviser to the White House on global AIDS issues.*

### **"Tennessee Voices: AIDS here and abroad offers us an opportunity"**

**Date:** 27 May 2007

**Source:** *The Tennessean*

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

<http://www.tennessean.com/apps/pbcs.dll/article?AID=/20070527/OPINION03/705270368/1097>

When I began doing AIDS research 20 years ago, we believed this epidemic was limited to gay men. Blacks sighed with relief that it would not affect them as so many other STDs did. Both of these notions were incorrect.

AIDS is a pandemic of historic dimensions. Most people affected are poor with little medical care. Most of the 20 million who have died, the 40 million infected and virtually all of the 12 million children orphaned are persons of color. With 40,000 new U.S. infections each year, HIV/AIDS is ravaging blacks - 13 percent of the population but 50 percent of AIDS cases.

The AIDS problem at home presents our nation with a historic opportunity for diplomacy. Human history is recounted through wars and disease with occasional promises of peace, health and prosperity. While our daily headlines seem to contradict our civilized progress, we live in an unprecedented time of order - at least in relation to where we have been.

No one can deny the atrocities and horrors that humans have committed upon each other - genocides, inquisitions, holocausts and enslavement - but I believe that we cannot deny the lessons learned over thousands of years of human development:

People are less inclined to war when they are happy and healthy.

Every battle between humans stems from the reality or fear of economic disaster, plagues and a shrinking future. Our world is no different than 5,000 years ago except for one thing: We understand disease.

Health research gives America the foundation for our global prominence; we are inoculated against epidemics, sanitized against plagues and educated against malnutrition. We have inequities of health care in our cities and countrysides, but our citizens are not threatened by death from malaria, tuberculosis, cholera or dysentery.

Daily, 28,000 children die from preventable conditions - more than 10 million a year. In the US, 7 in 1,000 die before age 5; in Iraq, 125, Nigeria, 194, Afghanistan, 257, Angola, 260. Globally, too many children do not live long enough

to contribute to their societies.

Every solution for a healthier America is an opportunity for diplomacy against the global image of imperial America. Rather than negotiating between economic sanctions and military force, we could already have allies. What changes could happen if America preferred a diplomacy of health rather than intimidation, and people of the world could say "they helped heal our children"?

Our democracy responds to the people when the will of the people is strong enough to demand a response. If we remove disease from our neighbors' struggles, then our security is better ensured than by the military alone; we will have fewer enemies with which to struggle.

Solving the domestic HIV problem with successful vaccines or **microbicides** serves the global interest and requires a global research effort. I encourage Tennesseans to join the national voice urging governmental support of global health research as a diplomatic strategy for peace. We have the opportunity to become heroes of civilization by increasing what we know and sharing what we learn.

### "Solution in a tube"

**Date:** 25 May 2007

**Source:** *Financial Mail*

**Author(s):** Charlene Smith

<http://free.financialmail.co.za/07/0525/features/afeat.htm>

SA is the first African nation to make a major investment into HIV/Aids clinical trials, namely those involving **microbicides** - medicines that prevent HIV/Aids infection through the use of mainly gels. So far R3bn/year has been dedicated to public-sector **microbicide** trials and this expenditure is set to rise with a major trial beginning in Durban this month and 16 more to be launched before end-2008.

The trials have government's backing. "Mathematical modelling has calculated that if a 60%-effective product were offered to 73 lower-income countries and used by 20% during half of unprotected sex acts, this would result in 2,5m HIV infections being averted in the first three years after the **microbicide** was introduced," says science & technology deputy minister Derek Hanekom.

According to UNAids statistics for 2006, 17,7m women worldwide are HIV-infected. Sixty percent of them live in sub-Saharan Africa and 34% of global Aids deaths happen here.

**Microbicides** are chemicals, usually in a gel, inserted into a woman's genital tract. An effective **microbicide** may also work against other sexually transmitted infections and, in some formulations, act as a contraceptive. "There are 3,5bn uninfected women in the world; married women are also at high risk of infection," Hanekom says.

**Microbicide** clinical trials are expensive, needing anything from 1 000 to 12 000 participants over the three phases

required to test each formulation. These cost US\$40m- \$70m, according to industry magazine *Microbicides Quarterly*. The cost of the trials in SA this year is conservatively estimated at R3bn, which is the amount devoted by major aid agencies and health bodies, such as UNAids and the Gates Foundation, to them.

In addition to these public-sector trials, pharmaceutical companies, both local and multinational, spend almost as much in clinical trials in SA, given that, apart from the prevalence of the disease in SA, the country also has a formidable medical research foundation and world-class laboratories. These investments will have a huge impact, says the Rockefeller Foundation's **Microbicide** Initiative, which estimates that **microbicides** will have a "peak market of \$5bn/ year".

By that estimate, the \$20m phase 2 clinical trial into a Tenofovir-based gel, a third-generation **microbicide**, is inexpensive. The trial began this month and is run by the Centre for the Aids Programme of Research in SA (Caprisa) in Durban, using 1 000 women.

Third-generation **microbicides** using antiretrovirals (ARVs) are expected to have a market share of \$274m of the total \$5bn in successful preventative HIV/Aids products. Third-generation **microbicides** are inhibitors that deactivate the virus as it tries to grow within cells by blocking an enzyme the virus needs to establish itself within the body. Unlike previous **microbicides** that had to be applied an hour or two before sex, the Tenofovir gel can be applied 12 hours before sex. It also has a low rate of resistance - only eight out of 299 patients treated with a combination therapy develop resistance after three years. It has almost no side effects.

The Caprisa 004 **microbicide** trial is the first major global ARV-embedded **microbicial** gel trial. It is also the first without supervision from a US or European government or development organisation. It is run almost entirely by South Africans under Prof Salim Abdool-Karim, one of SA's most distinguished Aids scientists, and his wife, epidemiologist Prof Quarraisha Abdool-Karim. Salim Abdool-Karim heads Caprisa and is pro vice-chancellor (research) at the University of KwaZulu Natal. He is also a member of the department of epidemiology at Columbia University in New York and the department of medicine at Cornell University.

The SA government's investment, through its biotechnology arm, LIFElab, is a modest R8,5m over four years but has allowed the Abdool-Karims to leverage funding from the US organisation, Family Health International. LIFElab CEO Blessing Okole insisted that Caprisa 004 be granted a non exclusive licence by the US licensor of the product to allow LIFElab, or another manufacturer, to supply the **microbicide** cheaply to Southern African Development Community countries. Salim Abdool-Karim says the mark-up on sales will be 5%-10%, with no royalties to intellectual property patent holder Gilead Sciences.

Jennifer Nadeau of the US-based **International Partnership on Microbicides** (IPM) told the FM that her organisation had 11 SA sites for **microbicide** trials starting in 2008. A further five would begin under the auspices of the US National Institutes of Health soon. Says Nadeau: "The antiretroviral likely to go into phase 3 first is Dapirivine, developed by Tibotec, part of Johnson & Johnson. We have negotiated a royalty-free licence so that the drug can be made available cheaply in developing countries, if we are successful in developing it into a **microbicide**. "Our funders are 11 European and North American governments, the EU and the Rockefeller and Gates foundations. Most of this is core support rather than funding for any particular trial."

The IPM, which oversees global **microbicide** research, is also looking for SA companies to manufacture successful **microbicides**. Health innovation manager at the department of science & technology, Glaudina Loots, says: "At the moment I am aware of two companies, Fresenius-Kabi and Adcock Ingram, that are capable of filling plastic applicators [for the gel]." SA's capacity to manufacture **microbicides** still needs to be determined. At the end of 2005 there was only one US Federal Drug Administration-approved pharmaceutical active ingredient manufacturer in SA - Fine Chemicals Corp.

Explaining the need to spread the benefits of **microbicides**, Salim Abdool-Karim says: "Many religious and cultural groups believe vaginal secretions are dirty" - they are in fact the vagina's most potent protection. Women dry the vagina with herbs because some men prefer dry sex - which tears the vagina and makes infection easier. Women also use bleach or Dettol, lemon juice, or damaging disinfectant soaps and even Coca-Cola. "Such damage aids lethal infections. For example, one in 29 SA women has cervical cancer, one of the highest rates in the world," Abdool-Karim adds.

A significant part of pre clinical trial preparation and counselling is to encourage women not to douche or use herbs, and to use condoms with the **microbicide**. But, says Abdool-Karim: "A **microbicide** will never replace safe sex and preventions." Indeed, the US National Institutes of Health has pointed out that a successful HIV vaccine could be rendered redundant if there is no behaviour change: no palliative will succeed without safe-sex practices.

Women remain particularly at risk. The 2006 Stats SA adult mortality report shows that between 1997 and 2004, death rates for females aged 20- 39 more than tripled, and for males aged 30- 44, more than doubled. Female death rates peak at age 30-34. The leading cause of these deaths is HIV/Aids.

At Vulindlela clinic outside Durban, one of the two trial sites for Caprisa 004 (the other is in central Durban), Quarraisha Abdool-Karim found HIV-infection rates alarmingly high: in 2004 55% of those aged 20- 24 were HIV-positive (compared with 44% in 2001); 66% (31% in 2001) of those aged 25- 29; 54% (14%) of those aged 30- 34; and 10% (16%) of those older than 35.

SA Medical Research Council president Prof Anthony Mbewu notes: "We have 500 000 new [HIV] infections each year, of which about 200 000 are women aged younger than 25. A **microbicide** could protect 100 000 women a year, even if it were only 50% effective."

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

**"Biomarkers of semen in the vagina: applications in clinical trials of contraception and prevention of sexually transmitted pathogens including HIV"**

**Author(s):** Mauck CK, Doncel GF, Biomarkers of Semen Exposure Clinical Working Group

**Reference:** N/A 75(6):407-19.

**Published Abstract:** Biomarkers of vaginal exposure to semen, long used in forensic medicine, are now becoming important in the development of vaginal **microbicides** to prevent HIV/STIs and the development of contraceptives. Semen biomarkers could help evaluate the safety of a new physical or chemical barrier, give preliminary indication of the effectiveness of physical barriers such as diaphragms or condoms, and provide information on unprotected intercourse among participants in a clinical trial who have been advised to use condoms. Candidate biomarkers of semen exposure fall into two broad categories: (1) biomarkers of seminal plasma, among which prostate-specific antigen (PSA) is the best characterized; and (2) biomarkers of spermatozoa and other cells present in semen. This paper, authored by a working group of investigators performing research in the field of semen biomarkers, summarizes the characteristics of an ideal semen biomarker, reviews preclinical and clinical data on existing and potential biomarkers, and outlines the steps that should be carried out to develop an improved biomarker of semen exposure.

**"Pharmacokinetic study to compare the absorption and tolerability of two doses of levonorgestrel following single vaginal administration of levonorgestrel in Carraguard(R) gel: a new formulation for 'dual protection' contraception"**

**Author(s):** Sitruk-Ware R, Brache V, Maguire R, et al

**Reference:** N/A 75(6):454-60.

**Published Abstract:** OBJECTIVE: The study was conducted to assess levonorgestrel (LNG) serum levels achieved after a single administration of two different doses of Carraguard **vaginal gel** containing LNG (CARRA/LNG), designed for use as **microbicide** and contraceptive for potential dual protection. MATERIALS AND METHODS: This was a randomized double-blind pharmacokinetic study conducted in 12 subjects enrolled at two centers. Each subject received a single vaginal administration of CARRA/LNG containing either 0.75 or 1.5 mg LNG per 4 mL of gel on Days 10-12 of the menstrual cycle. LNG serum levels were measured at 0, 1, 2, 4, 8 and 12 h after administration and for the following 7 days. LH and progesterone (for a preliminary evaluation of effect on the ovarian function) as well as SHBG were measured in the daily samples. RESULTS: Serum LNG maximum concentrations (C(max)) were 14.1+/-2.1 and 11.7+/-2.7 nmol/L and T(max) was 12.0 and 6.0 h for the low and high dose, respectively, with large intersubject variability within the first 48 h. Mean levels at 96 h were 10% of C(max). Differences in AUC between both doses were not statistically significant. SHBG levels decreased approximately 25% by Day 4 after administration. Luteal activity was observed in 3/6 and 5/6 of the subjects in the low- and high-dose group, respectively. CONCLUSION: This study demonstrates that the CARRA/LNG gel can sustain elevated serum levels of the contraceptive steroid for up to 96 h after a single application. The serum levels attained with the 0.75-mg formulation are in the range expected to perturb the ovulatory process as observed in some subjects. The lack of correlation between the administered dose and serum concentrations of the steroid may be related to a rate-limiting absorption of LNG from the vaginal mucosa. The results reported here suggest that the CARRA/LNG formulation has good potential to become a dual-protection method, possibly preventing conception and sexually transmitted infections.

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

##### "Electron tomography of the contact between T cells and SIV/HIV-1: Implications for viral entry"

**Author(s):** Sougrat R, Bartesaghi A, Lifson JD, et al

**Reference:** N/A 3(5):e63.

<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1864992>

**Published Abstract:** The envelope glycoproteins of primate lentiviruses, including human and simian immunodeficiency viruses (HIV and SIV), are heterodimers of a transmembrane glycoprotein (usually gp41), and a surface glycoprotein (gp120), which binds CD4 on target cells to initiate viral entry. We have used electron tomography to determine the three-dimensional architectures of purified SIV virions in isolation and in contact with CD4+ target cells. The trimeric viral envelope glycoprotein surface spikes are heterogeneous in appearance and typically  $\sim 120$  Å long and  $\sim 120$  Å wide at the distal end. Docking of SIV or HIV-1 on the T cell surface occurs via a neck-shaped contact region that is  $\sim 400$  Å wide and consistently consists of a closely spaced cluster of five to seven rod-shaped features, each  $\sim 100$  Å long and  $\sim 100$  Å wide. This distinctive structure is not observed when viruses are incubated with T lymphocytes in the presence of anti-CD4 antibodies, the CCR5 antagonist TAK779, or the peptide entry inhibitor SIVmac251 C34. For virions bound to cells, few trimers were observed away from this cluster at the virion-cell interface, even in cases where virus preparations showing as many as 70 envelope glycoprotein trimers per virus particle were used. This contact zone, which we term the "entry claw", provides a spatial context to understand the molecular mechanisms of viral entry. Determination of the molecular composition and structure of the entry claw may facilitate the identification of improved drugs for the inhibition of HIV-1 entry.

##### "Global Fund grant programmes: an analysis of evaluation scores"

**Author(s):** Radelet S, Siddiqi B

**Reference:** N/A 369(9575):1807-13.

**Published Abstract:** Background: The Global Fund to Fight AIDS, Tuberculosis and Malaria evaluates programme performance after 2 years to help decide whether to continue funding. We aimed to identify the correlation between programme evaluation scores and characteristics of the programme, the health sector, and the recipient country. Methods: We obtained data on the first 140 Global Fund grants evaluated in 2006, and analysed 134 of these. We used an ordered probit multivariate analysis to link evaluation scores to different characteristics, allowing us to record the association between changes in those characteristics and the probability of a programme receiving a particular evaluation score. Findings: Programmes that had government agencies as principal recipients, had a large amount of funding, were focused on malaria, had weak initial proposals, or were evaluated by the accounting firm KPMG, scored lowest. Countries with a high number of doctors per head, high measles immunisation rates, few health-sector donors, and high disease-prevalence rates had higher evaluation scores. Poor countries, those with small government budget

deficits, and those that have or have had socialist governments also received higher scores. Interpretation: Our results show associations, not causality, and they focus on evaluation scores rather than actual performance of the programmes. Yet they provide some early indications of characteristics that can help the Global Fund identify and monitor programmes that might be at risk. The results should not be used to influence the distribution of funding, but rather to allocate resources for oversight and risk management.

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## 5. EPIDEMIOLOGY

### "India finance minister says AIDS cases underreported"

**Date:** 23 May 2007

**Source:** *Reuters*

<http://www.alertnet.org/thenews/newsdesk/DEL134081.htm>

The number of people suffering from HIV/AIDS in India, the country with the world's highest caseload, could be more than the official count as many cases are not reported or detected, the finance minister said on Wednesday.

India has 5.7 million people living with HIV/AIDS, according to the United Nations. The state-run National Aids Control Organisation (NACO), which spearheads the country's fight against the deadly HIV virus, estimates 5.2 million cases. NACO figures do not include people below 15 years and above 49 years of age.

"All reports indicate it (HIV/AIDS) is under-reported and under-detected in the country," Finance Minister Palaniappan Chidambaram told a corporate awards ceremony. "We now recognise it is a serious problem and it is good now we are not in a state of denial anymore."

AIDS activists say a lack of awareness and widespread stigma has contributed to paranoia among many people about the virus and forced thousands of patients to hide their infection. Many people, including some federal lawmakers, believe that a person can get HIV by shaking hands with an infected person, surveys have shown. "Some hospitals and many families do not report HIV cases because of social stigma and this should be taken into account," said Denis Broun, UNAIDS chief in India.

Some experts say that if India's HIV epidemic does not stabilise, it could impact long-term economic prospects as many of those who are HIV-positive are in their twenties and thirties, ages seen as most productive in their jobs.

NACO estimates that out of 165,000 reported AIDS deaths so far, around 50,000 were in the 15-29 year age group.

## 6. POLITICS AND POLICY

### "Bush requests \$30 billion to fight AIDS"

**Date:** 31 May 2007

**Source:** *The New York Times*

**Author(s):** Sheryl Gay Stolberg

[http://www.nytimes.com/2007/05/31/washington/31prexy.html?\\_r=1&oref=slogin](http://www.nytimes.com/2007/05/31/washington/31prexy.html?_r=1&oref=slogin)

President Bush called Wednesday for Congress to spend \$30 billion to fight global AIDS over the next five years, a near doubling of financing that is part of a White House effort to burnish Mr. Bush's humanitarian credentials before he meets leaders of the Group of 8 industrialized nations next week.

The initiative, if approved, would build on a program that grew out of the president's 2003 State of the Union address, when he asked for \$15 billion over five years for prevention, treatment and care of AIDS patients in developing countries. Congress approved more than \$18 billion, but the program is set to expire next year.

Mr. Bush's announcement, delivered in the White House Rose Garden, adds to what has become an unexpectedly high priority for the White House. AIDS was not a signature issue for Mr. Bush when he ran for office in 2000. But it has become one in part because the Christian conservatives who make up his political base have embraced it, and in part because Mr. Bush wants to build a legacy for the United States and a more compassionate image abroad to counter international criticism of American policies in the wake of the Sept. 11, 2001, attacks.

That sentiment was reflected in Mr. Bush's remarks on Wednesday. "Once again, the generosity of the American people is one of the great untold stories of our time," he said. "Our citizens are offering comfort to millions who suffer, and restoring hope to those who feel forsaken."

AIDS advocacy organizations praised Mr. Bush for proposing the additional money, but said the plan which he said would provide drugs for 2.5 million patients did not go nearly far enough toward meeting the international community's stated goal of treating the estimated 10 million patients in developing nations. "It's a modest increase, it's important that he reaffirmed it, but we will need the next president to do more," said Paul Zeitz, executive director of the Global AIDS Alliance, a nonprofit advocacy group. "We're not getting ahead of the AIDS crisis. We're tempering it."

Administration officials concede that point and say the White House is hoping Mr. Bush's announcement will prod other Group of 8 countries, as well as nations that have growing economies, to make spending commitments of their own. "The goal of universal access isn't a United States goal, it's a global goal," said Mark R. Dybul, the administration's global AIDS coordinator. "The rest of the world is going to need to respond if we are going to achieve these goals."

International development and human rights issues will be high on the agenda of next week's summit, but so will climate change an issue on which Mr. Bush finds himself at odds with his fellow Group of 8 leaders, notably the

meeting's host, Chancellor Angela Merkel of Germany. Dan Bartlett, counselor to Mr. Bush, said the president intended to address climate change in a speech on Thursday at the United States Agency for International Development.

But so far this week, Mr. Bush has been devoting most of his attention to human rights and poverty, issues that draw him less criticism than his stance on climate change. In an interview Monday night, a senior administration official said Mr. Bush planned to spend the week in advance of the Group of 8 conference spotlighting humanitarian issues and "demonstrating U.S. leadership around the world."

On Tuesday, Mr. Bush announced he was imposing stiff economic sanctions on Sudan to press its government into cooperating with a United Nations peacekeeping force that is trying to end the violence in Darfur.

On Wednesday, in addition to the AIDS announcement, Mr. Bush named Robert B. Zoellick, his former trade representative, as his candidate to head the World Bank, calling the nominee "a committed internationalist" who "wants to help struggling nations defeat poverty." In Thursday's speech, Mr. Bush also intends to talk about education programs in the developing world, and his initiative to combat malaria.

The AIDS initiative, which is likely to generate bipartisan support in Congress, would cover federal spending for the 2009 to 2013 fiscal years, meaning the vast majority of the money would be spent after Mr. Bush left office. To promote it, the White House is sending Laura Bush to Africa next month. "She and I share a passion," Mr. Bush said. "We believe that to whom much is given, much is required."

The United Nations reports that there are nearly 40 million people worldwide living with H.I.V., the virus that causes AIDS; last year three million died from their infections. In his announcement in 2003, Mr. Bush said he was committed to offering treatment for two million H.I.V. patients by 2008. But so far, he said, the program, called the President's Emergency Plan for AIDS Relief, has paid for treatment for just 1.1 million people in 15 nations.

Advocates complain that the new goal, bringing the number of patients treated to 2.5 million, is not that much more ambitious than the old one. "By 2013 there will be 12 million people that urgently need medicines," Mr. Zeitz said.

The White House, however, said that in addition to providing treatment for 2.5 million, the new money would prevent 12 million new infections and provide care for more than 12 million people.

Mr. Bartlett said the president was convinced America's image in the world would improve because of it.

"I've heard him talk about this is a part of America that gets overlooked," he said, "and that over time, people will look back and say, 'At a point in time where America may have been under scrutiny for other reasons, look at the significant contribution they have made. They saved more lives than anybody could have imagined.' "

**"Brazil offers to provide technology, training for proposed pharmaceutical plant to produce HIV/AIDS, malaria drugs in Mozambique"**

**Date:** 30 May 2007

**Source:** *Kaiser Daily HIV/AIDS Report*

[http://www.kaisernetwork.org/daily\\_reports/rep\\_index.cfm?DR\\_ID=45221](http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=45221)

Brazil has prepared a study to determine the feasibility of constructing a \$23 million pharmaceutical plant in Mozambique to produce drugs for HIV/AIDS, malaria and other diseases, an unnamed spokesperson for Brazil's Ministry of Health said on Tuesday, Reuters reports. The spokesperson also said that Brazil has offered to provide technology, training and quality monitoring for the plant.

The offer to study the possibility of building the plant initially was raised in 2003 by Brazilian President Luiz Inacio Lula da Silva, who said he wanted drugs from the plant to be available to other African countries. The Brazilian ambassador to Mozambique Leda Lucia Camargo recently presented the study to Mozambique's government, Reuters reports.

Although previous reports indicated that Brazil offered to build the facility, the country has only carried out a study and had not offered to fund the plant, according to the spokesperson. "Brazil has no commitment to finance the construction," the spokesperson said, adding that France, Germany and Italy have expressed interest in helping to fund the plant, but a decision has not been made.

Mozambique's Health Minister Ivo Garrido said the government will decide next month whether to approve the Brazilian proposal. "We will have to study it very carefully," he said. About 1.6 million people are living with HIV in Mozambique, which has a population of 18 million people. Only a small number of people in need of antiretrovirals have access to the drugs, most of which are imported from India, according to Reuters (Reuters, 5/29).

### **"Slump in NIH funding is taking toll on research"**

**Date:** 28 May 2007

**Source:** *The Washington Post*

**Author(s):** Christopher Lee

<http://www.washingtonpost.com/wp-dyn/content/article/2007/05/27/AR2007052700794.html?referrer=email>

Stanford University biochemist Roger D. Kornberg won a Nobel Prize last year for work he began in the 1970s, but he is pretty sure that if he had been born a generation later, he never would have had the chance.

The scientist, 60, is convinced that his groundbreaking research, in which he figured out how information in the DNA of a gene is copied to provide instructions for building and running a living cell, would never have gotten the necessary funding support in today's tight budget environment at the National Institutes of Health. "In the present climate especially, the funding decisions are ultraconservative," he said in an interview. "If the work that you propose to do isn't virtually certain of success, then it won't be funded. And of course, the kind of work that we would most like to see take place, which is groundbreaking and innovative, lies at the other extreme."

Kornberg, who testified before a Senate committee this month, is one of a growing number of high-profile biomedical researchers who are buttonholing members of Congress, cajoling the Bush administration and generally sounding the alarm over what they see as a slump in NIH funding that is starving important projects of cash and driving young scientists away from research careers. That, they say, is undermining prospects for scientific breakthroughs of the sort that have led to new treatments for cancer, heart disease and diabetes, and raised hopes for tackling Alzheimer's disease and spinal cord injuries. "Unless we pursue these basic discoveries, we're going to really miss fundamental understandings of disease processes," said Joan S. Brugge, the head of the department of cell biology at Harvard Medical School, who appeared in March before the Senate Appropriations labor, health and human services subcommittee.

NIH officials do not dispute that times are tough, especially in light of rising federal deficits and spending on antiterrorism efforts and the wars in Iraq and Afghanistan. "The pot of discretionary funding is not very large, relatively speaking, and there are a lot of competing priorities for it," said Norka Ruiz Bravo, NIH deputy director for extramural research.

At the heart of the problem, scientists say, is not merely the absolute level of funding for the NIH, the primary federal agency sponsoring and conducting medical research. Rather, it is the way funding levels have fluctuated dramatically -- with big increases followed by periods of stagnation -- instead of climbing predictably to allow for sound research planning. Congress nearly doubled NIH's budget -- to \$27.1 billion between 1998 and 2003 -- as officials sought to capitalize on new lines of research opened up by the Human Genome Project. Medical schools and other research institutions responded accordingly, adding faculty and beginning construction on new facilities. At the same time, the number of grant applications rose 44 percent, from 24,151 in 1998 to 34,710 in 2003. But eventually the flood of new cash slowed to a trickle. At \$28 billion, the NIH's fiscal budget for 2004 was only 3.3 percent higher than the previous year's. President Bush has recommended \$28.9 billion for fiscal 2008 -- \$379 million less than the NIH got this year, according to agency figures. Moreover, because the budget would increase by \$201 million the government's contribution through NIH to an international AIDS fund, the reduction for research in 2008 actually would be more than \$500 million.

A flat budget, plus rising demand for new research dollars, equals plenty of angst in laboratories and science departments across the country. Although the number of grant applications has continued to rise, the percentage that win federal funding has shrunk from 32.1 percent in 2001 to 20 percent in 2006, according to NIH figures. Researchers say the situation is worse than those figures suggest. Many established scientists are having to submit grant applications two or three times before getting an award, and success rates for applications from younger researchers are in the single digits.

"It is really a very scary, sad situation out here," said E. Chester Ridgway, head of endocrinology at the University of Colorado at Denver and Health Sciences Center. Ridgway said a tenured professor in his mid-50s who directs a training program in cancer pathology there recently learned that none of the three NIH grants that support his research would be renewed. "In previous years, he would have anticipated renewing all of them," he said. "That's his only source of support. I don't know what this guy is going to do." In the endocrinology division, four young research fellows who were unable to land a crucial first grant decided to abandon research for careers in medicine or industry,

Ridgway said. "They don't come back after they do that," he said. "I was very distressed by that."

Ruiz Bravo, the NIH official, said the agency is trying to mitigate the effects of a budget that has been "flat" since 2003 with new programs that help first-time investigators get a shot at grants and other initiatives to funnel funding to more established researchers. "In terms of purchasing power of the dollar, it is in fact a reduction in the overall NIH budget," she said. "That's just the reality of it. So when investigators feel the pinch, it's a real pinch."

Of course, supporters of other federal agencies that could not dream of having their budgets double over five years might wonder whether the ruckus is an overreaction. Brent L. Iverson, a professor of chemistry and biochemistry at the University of Texas at Austin, said it's not a fair comparison. "Science and research and engineering research is different, because that's the engine that drives the economy," Iverson said. "Several billion more dollars spent on Medicare is not going to solve the Medicare problem. But it is quite possible that that same amount of money invested in medical research may create the breakthrough which helps solve the Medicare problem."

Help may be on the way. In a March 6 hearing, Rep. David R. Obey (D-Wis.), chairman of the House Appropriations Committee, noted that the Democratic-controlled Congress increased the NIH's fiscal 2007 budget by over \$600 million more than Bush requested. He pledged to increase it again for fiscal 2008, although he gave no specifics. "I'd suggest that the investments that you're talking about in this area are tremendously important -- not just to the public's health, but also to the productivity of the economy," Obey said during the hearing. "Healthy people are a whole lot more productive than sick ones."

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