



ALLIANCE FOR MICROBICIDE DEVELOPMENT

23 February 2007, Volume 8, Number 7

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. 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. ALLIANCE UPDATES AND COMMUNITY NEWS

The Alliance welcomes our new Communications Associate

The Alliance is pleased to welcome our new Communications Associate, Latifa Boyce. Latifa holds a BS in Biology from Howard University, an MPH in Epidemiology and Biostatistics from the George Washington University, and is currently completing an MA in Health Journalism from the University of Minnesota. Prior to joining the Alliance as our Communications Associate, Ms. Boyce worked as public health communicator and researcher for various organizations, including the National Institutes of Health (NIH), Center for Infectious Disease Research and Policy (CIDRAP), Pacific Institute for Research and Evaluation (PIRE) in Calverton, Maryland, and National Minority AIDS Education and Training Center (NMAETC) at Howard University. Ms. Boyce has extensive experience developing and evaluating public health campaigns, liaising with the media, and writing and producing stories for television and print media outlets. Prior to focusing her career on health communications and journalism, Ms. Boyce worked as an epidemiologist where she performed analyses of state mortality and morbidity data to determine the distribution and causes of injuries. Ms. Boyce has presented her research at several professional meetings, including the American Public Health Association (APHA), North American Congress of Clinical Toxicology (NACCT), and National Center for Health Statistics (NCHS) Data Users Conference and at the Institute of Medicine (IOM).

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2. MEDIA COVERAGE OF MICROBICIDES

"Women missing after drug trial"

Date: 22 February 2007

Source: News 24

Author(s): Sydney Masinga

http://www.news24.com/News24/South_Africa/Aids_Focus/0,,2-7-659_2073394,00.html

Thirteen women who participated in a medical trial to test the effectiveness of an anti-HIV/Aids gel, or **microbicide**, have gone missing. They may now have HIV and not know it. Some 20 women from KwaZulu-Natal have already tested positive when the gel failed to work and they failed to use condoms that were given to them free of charge. The women were HIV negative when the trial started.

Principal researcher at the Medical Research Council in Durban, Dr Roshini Govinden, said 98% of the 604 women from KwaZulu-Natal and the Western Cape who participated in the trial had been traced. "The remaining 2% gave us the wrong contact information when we started the tests, so we are struggling to locate them now," she explained on Wednesday.

The trial was conducted by the MRC and an American company called Conrad.

Paid R150 each

Conrad is also testing the gel in other third world countries, namely India, Uganda and Benin. The trial was stopped in all countries in the final phase of tests because 35 of the 1 333 participants contracted HIV.

Govinden denied that poor black women in third world countries were used as human guinea pigs. "People should understand that **microbicides** are manufactured in first world countries like the US and in Europe, but they are not brought to South Africa to make people guinea pigs. The trial goes through three phases and they are brought to the poor countries in their last phase," she explained.

She said the first phase involved tests in laboratories and on animals, the second phase involved testing on only a few humans in the country where the drug was made to see if it worked. Govinden said there were 11 successful trials of the gel on five women and two men in the United States and Europe before the tests were done on larger groups in third world countries. "The last phase is done in poor countries because they are the most affected and have the highest infections when it comes to HIV," she explained.

She said people in poorer countries were also more likely to practise high risk behaviour by not using condoms. "So it make sense to do the last phase in countries where more people are at risk of contracting HIV," she explained. The MRC and Conrad are presently doing three other trials on **microbicides**, with the support of the national department of health.

Govinden said participants must be HIV negative, older than 18, not pregnant and sexually active. She said the consent forms in KwaZulu-Natal were translated into isiZulu to ensure participants understood the process and risks. They were also shown a flip chart and given a test to check that they understood the trial. "They had to get a 100%

pass rate to participate in the trial. If you get less than that, then you don't really understand, so you are out," she said.

Govinden said the participants were paid R150 each, not as a payout or bribe, but because it was the standard rate set by the MRS for any drug trial in the country, not just those for **microbicides**.

"Failure of HIV microbicide raises concerns"

Date: 21 February 2007

Source: *The Scientist*

Author(s): Andrea Gawrylewski

<http://www.the-scientist.com/news/home/52861/>

A **microbicide** designed to ward off HIV is unexpectedly linked to an increased risk of infection, prompting speculation about the future of **microbicides** against HIV.

Researchers shut down an HIV **microbicide** clinical trial last month in Africa and India after early data indicated **microbicide** users had a higher rate of infection than women using a placebo. The discouraging results have surprised and disappointed researchers, and may ultimately have a negative impact on the future role of **microbicides** in preventing the spread of the virus.

Several other **microbicides** are in the pipeline for testing and development, but this trial failure may push some researchers in the direction of other HIV prevention options, predicted Daniel Kuritzkes, director of AIDS research at Brigham and Women's Hospital. "The field is moving towards more specific approaches -- use of topical applications of antiviral drugs, as opposed to true **microbicides**," he told *The Scientist*. "The [closed trial's] results would make me less enthusiastic about pursuing other [**microbicides**]. I would be a bit leery about getting into **microbicide** studies."

Enrollment for the phase III trial for the cellulose-sulfate compound, called Ushercell, began in 2005. When it was stopped, the trial's preliminary analysis included 1,333 women in India, Uganda, Benin, and South Africa. Initial results showed that 35 women had contracted HIV while using the compound, a higher rate of infection than that seen in women using a placebo. CONRAD, the Arlington, Va.-based nonprofit reproductive health organization that funded the development and testing of Ushercell, halted the trial immediately.

The results were met with shock by researchers involved in the study. "We have no idea at all how to explain the mechanism in which there was an increase in infection," Lut Van Damme, who led the trial, told *The Scientist*.

"Nothing went wrong, the trial went according to all rules and regulations."

Ushercell, originally created by Polydex Pharmaceuticals, had successfully completed 11 safety and contraceptive trials involving more than 500 patients before entering the HIV-prevention trial.

CONRAD has invested nearly \$40 million to date on developing and testing Ushercell, estimated Executive Director Henry Gabelnick. The agency will continue to sponsor the investigation into what went wrong with Ushercell, but may re-direct funding to several other compounds still in development, Gabelnick said.

He added that he was very disappointed by the failed trial. "It was totally unexpected," Gabelnick told *The Scientist*.

"You invest so much time and effort. You plan for success."

The compound, in gel form, is inserted vaginally or anally one hour before intercourse. A previous trial suggested Ushercell could also work as a contraceptive.

Researchers involved in the trial will spend the remainder of the year collecting, cleaning, and analyzing the trial's data set. Still, Van Damme said she already anticipates that exploration into Ushercell as an HIV **microbicide** is over.

Polydex spokesperson Linda Hughes said that if further tests show Ushercell was not the cause of increased HIV infection, it could still have a life as a second generation **microbicide** or as an inert addition to an antiviral treatment. "It could be reconsidered," she told *The Scientist*, "but it wouldn't be what we'd hoped for."

Van Damme was also the head researcher of a study that tested nonoxynol-9, the controversial spermicide, as a **microbicide** against HIV. Results from that study also showed an increased rate of HIV infection among gel users, in that case due to lesions created by the gel. According to Van Damme, the current mystery surrounding Ushercell's failure is nothing like the trial of nonoxynol-9, which showed signs during preclinical experiments that it might not work as an HIV **microbicide**.

Population Council, a New York-based non-profit research organization that is also testing a **microbicide** against HIV, is already feeling some negative effects from the Ushercell trial, according to spokesperson Melissa May. She noted that sites that are set to finish the **microbicide** phase III trial at the end of March have received several concerned phone calls from trial participants about the safety of the compound following the news about Ushercell. "The fallout that has come, and the confusion as a result of the announcement [of the Ushercell trial closing], is piling on the disappointment," May told *The Scientist*. While results of the trial of the **microbicide**, called Carraguard, won't be available at least until the end of the year, an independent data monitoring committee evaluated the trial three times, and each time declared the compound was safe.

For now, Van Damme and her colleagues are left to sleuth out how Ushercell was associated with more cases of HIV in their trial subjects. But she said she believes that **microbicides** will continue to be a viable product for HIV prevention, and characterized the Ushercell episode as a learning experience. "Every trial which comes to an end, so to speak, always has some positive things," she said. "Maybe we'll learn something down the line. All in all, science will be served."

"South Africa: Research body head defends ethics of AIDS gel project"

Date: 21 February 2007

Source: *Business Day (South Africa)*

Author(s): Tamar Kahn

<http://allafrica.com/stories/200702210810.html>

Medical Research Council (MRC) president Anthony MBewu yesterday sought to reassure Parliament that the organisation's work on the international Ushershell **microbicide** trial, which was stopped early after 35 women developed HIV, had been conducted to the highest scientific and ethical standards.

With one of the world's worst HIV epidemics, SA is at the forefront of international efforts to develop safe and effective **microbicides**, gels or creams that women can use to help reduce the risk of catching the virus from infected male

partners. The Ushershell trial was in its final stages but was halted after interim analysis of the data showed the cellulose sulphate gel might raise the risk of getting infected with HIV. The news triggered widespread media coverage, with one weekend newspaper describing the South African trial participants as "guinea pigs".

The MRC had consequently stepped up its efforts to inform the public that the Ushershell trial had been conducted to the highest international standards, said MBewu. "There is a misconception that trials are undertaken to satisfy scientific curiosity or for money. People don't realise they should be done in SA," he said. Research should ideally include the population groups who would eventually use the products.

MBewu urged MPs to support the MRC's call for greater scrutiny of all clinical trials conducted in SA. Earlier this month the MRC suggested that the health department develop a clinical trials inspectorate working under the auspices of the National Health Research Ethics Committee. Although proposals to conduct clinical trials were carefully vetted by ethics committees at universities, and by the Medicines Control Council, there was little subsequent oversight by an independent authority, he said. However, the health department's new clinical trials registry was an important step towards providing the public with more information on the variety of research projects with human subjects, he said. The register, available on the internet, lists 159 clinical trials.

Two independent organisations oversaw the Ushershell research: the US-based health organisation Conrad was running trial sites in SA, Uganda, Benin and India; while Family Health International ran two trial sites in Nigeria. Women were given a **microbicide** or a dummy gel, as well as condoms and regular counselling about safe sex; neither they nor the researchers knew whether they were getting a placebo or the real product. A total of 1333 women were recruited by the Conrad trial, of whom 604 women were from SA; 20 of the South African women had developed HIV, but researchers did not yet know whether or not they had used the **microbicide**, said MBewu. Eleven previous trials of the Ushershell **microbicide** had found no adverse effects, so researchers were puzzled as to why so many women in the trial had got HIV, he said. Scientists were unlikely to have an explanation for several more months, he said.

Members of Parliament's portfolio committee on health questioned mBewu closely on the methods used to recruit participants for the Ushershell **microbicide** and whether the women had fully understood the risks and benefits involved in the research. MBewu said women were paid R150 for each visit to the research centre in Durban, but said this was not a "perverse incentive" as government policy required researchers to provide trial participants with a basic stipend to cover transport, lunch and lost income.

"Treat herpes, reduce HIV infections: study"

Date: 21 February 2007

Source: *CBC News*

<http://www.cbc.ca/health/story/2007/02/21/herpes-hiv.html>

Women infected with both HIV and genital herpes show lower levels of the AIDS virus in their systems if the herpes is treated.

Researchers tested 140 women in Burkina Faso who had both infections. More than 100 received a medication, valacyclovir, to treat herpes and the rest took placebo pills. "The results of the trial are striking," said the study's lead

author, Dr. Nicolas Nagot of the London School of Hygiene & Tropical Medicine. "They show that valacyclovir significantly reduces the frequency and quantity of HIV detectable in genital secretions and, in addition, reduces the quantity of HIV in the [blood]." The benefit appeared to grow stronger over the three months of follow up, the researchers said in Thursday's *New England Journal of Medicine*.

The findings could open new approaches to preventing the spread of HIV and managing patients who are infected by both viruses. It is estimated that 50 to 90 per cent Africans who have HIV also have the virus for genital herpes, HSV-2. Previous studies have shown that people with HIV and herpes show more viral replication and HIV cells in the blood and vaginal area. Doctors tended to put less emphasis on treating genital herpes because it is less dangerous than HIV.

Drugs affordable

Besides valacyclovir, the drugs acyclovir and famciclovir also can be used to treat HSV-2. All three drugs are relatively affordable and carry few side-effects, the researchers said.

In 2005, an estimated 4.1 million people were newly infected with HIV, mostly through heterosexual intercourse. The infections show that behavioural changes do not always work, so it is important to look for other ways to reduce the biological susceptibility to HIV, Nagot said. **Microbicide** gels that women could apply themselves without the knowledge of their partners and male circumcision are some of the strategies that are under investigation for preventing HIV infection.

EDITORS' NOTE: The journal article cited above, Reduction of HIV-1 RNA Levels with Therapy to Suppress Herpes Simplex Virus (Nagot et al.), can be found in the 22 February 2007 issue of The New England Journal of Medicine, Volume 356, Number 8, pages 790-799, available online at

<http://content.nejm.org/cgi/content/full/356/8/790>

"Bill Gates, Canada team up to fight AIDS"

Date: 20 February 2007

Source: *Agence France Presse*

http://www.eneews.ma/bill-gates-canada_i39193_6.html

Canada's Prime Minister Stephen Harper, who was blasted for shunning AIDS talks in 2006, and software mogul Bill Gates pledged funding Tuesday to accelerate the development of an HIV/AIDS vaccine. Ottawa will contribute 111 million Canadian dollars (95 million US) toward international research efforts and to build a Canadian facility to make vaccine candidates for use in clinical trials, while the Bill and Melinda Gates Foundation will provide 28 million Canadian dollars (24 million US).

The collaboration will "accelerate the pace towards the discovery of an HIV vaccine ... move vaccines to the clinical trial stage more quickly and improve access to an eventual vaccine," Harper told reporters. The result would spare "millions of people from the horrific reality of HIV-AIDS," he said. Bill Gates echoed Harper, saying the funding will "make a big difference."

"Most scientists think that it probably will take more than ten years (to create a vaccine). We could get lucky, it could happen sooner than that. But with all tough problems, the more energy we put into it, clearly that's going to cut down the amount of time required," he said.

Gates and his wife, in a keynote speech at the 16th International AIDS Conference in Toronto in August vowed that the mighty cheque-wielding charity that bears his name would make AIDS its top priority. In the run-up to the six-day AIDS meet that attracted 21,000 delegates, the Gates Foundation announced help of 500 million dollars to the Global Fund to Fight AIDS, TB and Malaria, bringing their pledges to the agency to 650 million dollars. This came only weeks after a contribution of 287 million dollars to speed the development of an HIV vaccine. The Foundation stumped up 60 million dollars for **microbicide** research in 2003, and 50 million dollars for Botswana in 2000. Harper meanwhile was criticized for not attending the conference and for postponing a much-anticipated AIDS funding announcement, until now.

"Biotech in promising deal"

Date: 20 February 2007

Source: *Herald Sun (Australia)*

Author(s): John Beveridge

Melbourne biotechnology group Starpharma has signed a US agreement that gives it world rights to a promising technology. In the first major deal since acquiring US-based Dendritic Nanotechnologies, Starpharma will now have an exclusive licence and supply agreement with Merck offshoot EMD Biosciences.

Speaking just before boarding a plane to meet US investors, chief executive Dr Jackie Fairley said research using the DNA and small interfering RNA (siRNA) was reaching an important point. "There are no drugs on the market yet using this research but there are some entering clinical trials," said Dr Fairley.

Potentially the laboratory research using reagents supplied by Starpharma could develop a different class of drugs that can turn off certain natural cell processes. That promises different therapies for treating cancer and diseases such as the eye complaint macular degeneration. Dr Fairley said it was a natural progression for processes tested in the laboratory to become novel human therapies.

There had also been some large acquisitions around the billion-dollar mark of siRNA technology. Under the deal Starpharma will produce reagents used in the laboratory testing, although the price and terms of the deal were not disclosed. Dr Fairley said she was looking forward to briefing US investors who now made up about 10.2 per cent of shareholders through the US ADR listing.

One of Starpharma's other products is VivaGel which has a significant contraceptive and sexually transmitted disease prevention effect. A vaginal **microbicide**, VivaGel has even proved largely effective in preventing conception in rabbits and is undergoing human trials in Africa, the US and Australia. Given HIV is such an important disease, the drug has been given fast-track status by the US Food and Drug Administration. That means it could potentially pass all of its regulatory hurdles by 2008-09. The gel may also prove to be effective against other sexually- transmitted diseases.

Starpharma, which is chaired by Peter Bartels, has several other projects at earlier stages of development using large molecules known as dendrimers. Starpharma shares yesterday closed steady at 51.

"Dominican prostitutes test AIDS vaccine"

Date: 18 February 2007

Source: *Associated Press*

Author(s): Jonathan M. Katz

<http://www.mercurynews.com/mld/mercurynews/living/health/16729242.htm>

Leaving her tin-roofed brothel for the day, the 42-year-old prostitute journeys to the capital for an injection that might save not only her life, but possibly millions more around the world. Jacinta Julia Adams Fernandez, a mother of three, is one of 175 Dominican prostitutes lending their bodies to a trial of what New Jersey-based Merck & Co. hopes will prove to be a vaccine against the virus that causes AIDS.

Since turning to prostitution after a divorce 13 years ago, Adams has seen friends and co-workers die from the disease. Prostitution is illegal but widespread here, largely ignored by the authorities. "It's rare for anyone who lives here not to know AIDS and what it can do," said Adams, a heavyset woman dressed for work in a tight-fitting yellow dress and bright red lipstick.

AIDS is the leading killer of people aged 15 to 44 in the Caribbean, claiming 24,000 lives in 2005, a rate second only to that of sub-Saharan Africa. And according to the United Nations, nearly three-quarters of those infected live on the island of Hispaniola, which the Dominican Republic shares with Haiti. At least 70,000 of the Dominican Republic's 9 million people are HIV positive, and discrimination discourages many from seeking testing or treatment. Among prostitutes, about 3.6 percent are infected, although researchers report rates as high as 12 percent in some areas.

The prostitutes, who will spend much of the next four years traveling to Santo Domingo for injections and checkups, were recruited from brothels across the country. They are among some 3,000 people in eight countries testing the experimental vaccine - a combination of deactivated cold viruses and synthetically produced HIV genes meant to train the body to destroy infected cells.

Any long-term risks will take years to discover, but once doctors explained there was no way to contract the disease from the vaccine, they found plenty of volunteers at Adams' brothel in Las Guaranas, a town of dirt streets and low-slung houses surrounded by rice fields about 75 miles north of Santo Domingo. Many were turned away because of pregnancy, conditions like high blood pressure or because they are already infected. Participants don't know whether they are getting the drug or a placebo. Even if the results are promising, a vaccine would be several years away from reaching the market.

The program pays the women's meals, transportation and \$30 for a lost day's work. A handful have dropped out, and the clinic provides health training and occasional gifts like bags of cosmetics to keep others from losing interest. Participants get three injections over their first seven months in the study, and then must keep reporting back for four years of close monitoring.

For many, the greatest reward is pride. "We are doing it for the world," said 38-year-old Lucila Mendoza Ovalle.

The other test sites - Haiti, United States, Australia, Brazil, Canada, Jamaica and Peru - all have the same strain of HIV, said Merck spokeswoman Janet Skidmore. The strain is also found in Europe, meaning a formula that works here could find a lucrative global market. A trial was launched Thursday in South Africa to see if the vaccine would have any effect on African strains.

The Merck trial, currently in the second of three testing phases - each of which is to last several years - is one of 17 sponsored by the HIV Vaccine Trial Network, a Seattle-based group supported by the U.S. government.

The trial is "is an extremely important step, but not the only one," said Dr. Jorge Flores, chief of vaccine research for the AIDS division at the U.S. National Institute of Allergy and Infectious Diseases. He stressed the importance of education and research into other strategies, like **microbicides** in **vaginal gels**.

Even a vaccine that reduces the level of HIV in future infections would be a victory. "A 90 percent, 80 percent reduction is going to be acceptable for the time being," said Dr. Ellen Koenig, who heads one of two Santo Domingo clinics testing the formula.

Margarita Ramirez de los Santos, 24, said she volunteered after her brother and sister-in-law died of AIDS. "I am worried about my health," she said.

Meanwhile, Adams' brothel insists on more familiar methods - condoms and frequent testing for HIV. And if a client refuses to use protection? "We kick him out," Adams says with a laugh.

"Uganda: Museveni scoffs at circumcision for HIV-AIDS"

Date: 18 February 2007

Source: *The Monitor*

Author(s): Agness Nandutu

<http://allafrica.com/stories/200702170370.html>

President Yoweri Museveni has trashed claims that circumcised men are less prone to HIV/Aids infection. Mr Museveni was on Thursday speaking to over 350 NRM district leaders and MPs from the central region at Vice President Gilbert Bukenya's Garuga home, off the Kampala-Entebbe highway.

In a press statement from Prof. Bukenya's office, Mr Museveni warned that immorality was leading to increased infection rates. "The only way to avoid getting infected is to avoid having illicit sexual affairs. Why are Muslims and Bagisu dying? Who beats the Bagisu when it comes to circumcising men?" Mr Museveni asked. Among the Bagisu, a tribe in eastern Uganda, every male, between adolescence and manhood, must be circumcised. The circumcision is done in the open during daytime, in the presence of witnesses.

Mr Museveni also scoffed at claims that the **microbicide** gels that have been on trial in various countries can be an effective prevention against HIV/Aids. "People know how and where they can catch Aids. Unless they fight irresponsible sexual relationships, they cannot stop it," he said.

United States researchers last month halted clinical trials of cellulose sulphate, a topical **microbicide** gel being tested for prevention of HIV/Aids infection in women. Preliminary data indicated that cellulose sulphate could lead to an increased risk of HIV infections in women who use the compound. The trial was being conducted in South Africa, Benin and India.

Mr Museveni said part of the NRM strategy was to keep Ugandans alive and in good health. He said his government had implemented immunisation programmes among children and sensitised the entire country about the HIV/Aids pandemic. The approach, he said, had helped reduce the rate of infection. The other approach, he said, was the doling out of ARV drugs to infected Ugandans in a bid to prolong their lives.

"Starpharma gets a US grant for HIV /genital herpes trial"

Date: 15 February 2007

Source: *Australian Associated Press*

http://www.medicalsearch.com.au/News/Starpharma_gets_a_US_grant_for_HIV_genital_herpes_trial-24211

Australian biotechnology company Starpharma Holdings Ltd has received a further grant from US health institutions to continue testing its HIV and genital herpes prevention drug. Starpharma on Tuesday signed an agreement with National Institute of Allergy and Infectious Diseases and National Institute of Child Health and Human Development for an undisclosed amount to conduct clinical trial of VivaGel in sexually active women. The drug, which is currently being trialled on 60 to 100 women in San Francisco and Kenya, will now be trialled on 40, 18 to 24-year-old women in Porto Rico and Florida. In October 2005, Starpharma received a \$US20.3 million (\$A26.36 million) grant from the institutions for HIV drug development and then in April 2006 a undisclosed grant for genital herpes drug development.

"Newer approaches to HIV prevention"

Source: *Lancet*. 2007 Feb 24;369(9562):615.

Author(s): Editorial

<http://www.thelancet.com/journals/lancet/full?volume=369&issue=9562>

The publication of two randomised trials in today's *Lancet* signals a new era for HIV prevention. The studies, in Uganda and Kenya, show that male circumcision halves the risk of adult males contracting HIV through heterosexual intercourse.

This success is extremely welcome news. The results of these trials, along with the findings of a preliminary South African trial published in 2005, now provide a solid evidence-base to inform health policy. Large-scale implementation of male circumcision has the potential to substantially reduce HIV transmission, particularly in sub-Saharan Africa. But, as an accompanying Comment and Viewpoint highlight, this new intervention presents many opportunities but also raises many questions.

One such question is the effect of male circumcision on women. Initially, wide-scale implementation of male circumcision will lower HIV infection in men. But modelling studies suggest that over time women could benefit from an effect similar to the herd immunity seen with mass immunisation. Male circumcision might also directly protect against male-to-female transmission of HIV. A trial to test this hypothesis is under way in Uganda, with results expected in 2008.

In the meantime, new approaches for HIV prevention in women are urgently needed. According to UNAIDS, during the past 2 years, the number of women and girls infected with HIV has increased in every region of the world. Although condoms can provide a high level of protection (80-90) against sexual transmission of HIV if used consistently and properly, many women are not in a position to persuade partners to use them. The development of new technologies that put HIV prevention in the hands of women is therefore crucial.

Microbicides-vaginally applied antimicrobial medications that can kill, block, or inactivate HIV-are one such intervention. According to a Review of **microbicide** drug candidates, published online by *The Lancet* on Feb 14, a large number of compounds-more than 60 at the start of 2006-are in the development pipeline. And, at the beginning of this year, five phase III trials testing different formulations were under way.

Sadly, however, the **microbicide** field was hit with bad news on Feb 1, when the International AIDS Society announced that two phase III trials of the candidate **microbicide** cellulose sulphate had been stopped because preliminary results suggested a potential increased risk for HIV in women who used the compound. At present, there is no explanation as to why cellulose sulphate was associated with a higher risk of HIV infection than placebo.

Although the halting of these trials is a disappointing setback for **microbicide** research, the investigators deserve praise for acting quickly as soon as an adverse effect became apparent. In the development of any new product, ruling out potential candidates is essential for progress. As for the remaining late-stage **microbicide** trials, if they prove successful, first-generation products could be available by 2009. If they fail, second-generation products could become available by 2012.

A much more distant hope for HIV prevention is the development of an effective vaccine that can offer long-term protection against the wide spectrum of HIV variants that exist. Despite the fact that there are now more than 30 vaccine candidates in clinical trials, and three of these are in advance stage testing (phase IIb and phase III), many obstacles still lie in the way of the development of a truly effective HIV preventive vaccine.

The genetic diversity of HIV presents an enormous challenge for researchers. And, because the virus has the ability to evade neutralising antibodies produced by natural immunity, the standard vaccine strategy of mimicking natural infection to induce antibodies has so far proved impossible. Strengthening cell-mediated immunity offers another possible route to success. About 90 of candidate HIV vaccines in development use this approach. These products will not prevent infection. But it is hoped that they will lower viral load and therefore progression to AIDS and secondary transmissions. Whether even this will be possible remains to be seen. Some observers believe that a vaccine to prevent HIV will never be achieved.

Ultimately, even if an HIV preventive vaccine or **microbicide** were to be developed, they are unlikely to be 100% effective. This prospect, together with the knowledge that male circumcision offers only partial protection against HIV infection, means that the future of HIV prevention will involve combining new methods with existing approaches, such as condom use. The emerging truth is that no single approach alone will be able to stem the spread of HIV.

3. PUBLISHED RESEARCH: MICROBICIDE-SPECIFIC

"Direct inactivation of HIV-1 by a novel small molecule entry inhibitor DCM205"

Author(s): Duong YT, Meadows DC, Srivastava IK, et al

Reference: N/A Epub ahead of print.

Published Abstract: With more than 40 million people living with HIV, there is an urgent need to develop drugs that can be used in the form of a topical **microbicide** to prevent infection through sexual transmission. DCM205 is a recently discovered small molecule inhibitor of HIV-1 that is able to directly inactivate HIV-1 in the absence of a cellular target. DCM205 is active against X4, R5 and dual tropic laboratory-adapted and primary strains of HIV-1. DCM205 binds to the HIV-1 envelope glycoprotein, and competition studies map the DCM205 binding at or near the V3 loop of gp120. Binding to this site interferes with the sCD4 interaction. With its ability to disable the virus particle, DCM205 represents a promising new class of HIV entry inhibitor that can be used as a strategy in the prevention of HIV-1/AIDS.

"Microbicide drug candidates to prevent HIV infection"

Author(s): Balzarini J, Van Damme L

Reference: N/A Epub ahead of print.

Published Abstract: 25 years after the first HIV/AIDS cases emerged in 1981, the disease continues to spread worldwide, with about 15,000 new infections every day. Although highly active antiretroviral therapy (HAART) has greatly reduced the rate of HIV infection, and the spread of the epidemic, this effect has largely been seen in developed countries. More than 90% of HIV-infected people live in developing countries, most of whom do not have access to this treatment. The development of efficient, widely available, and low-cost **microbicides** (gels and creams can be applied topically before sex) to prevent sexually transmitted HIV infections should be given high priority. We review different categories of **microbicide** drugs and lead compounds, their mechanism of action, current status of development, and progress in phase III trials.

"PRO 2000 elicits a decline in genital tract immune mediators without compromising intrinsic antimicrobial activity"

Author(s): Keller MJ, Guzman E, Hazrati E, et al

Reference: N/A 21(4):467-76.

Published Abstract: **OBJECTIVE:** Vaginal **microbicides** should protect against infection without disrupting the mucosal environment or its mediators of host defense. The objective of this study was to examine the effect of 14 daily applications of 0.5% PRO 2000 or placebo gel on mediators of mucosal immunity and intrinsic antimicrobial activity. **DESIGN AND METHODS:** A randomized, prospective, double-blind, placebo-controlled study was conducted

among 24 healthy, abstinent women. Levels of cytokines, chemokines, defensins, and other protective factors and intrinsic antimicrobial activity were determined in cervicovaginal lavage samples collected on study days 0, 7, 14, and 21. RESULTS: No increase in pro-inflammatory cytokines was observed. Rather cytokines and protective factors including interleukin (IL)-1 receptor antagonist, immunoglobulins and human beta-defensin 2 were lower in the drug compared with the placebo group. All of the mediators returned towards baseline on day 21. Women who were cycling had lower levels of most proteins on study days 7 and/or 14 compared with women on oral contraceptives; however, the magnitude of decline was greater in women who received PRO 2000 compared with placebo gel. The reduction in protective factors was not associated with a loss in the intrinsic anti-viral (HIV or herpes simplex virus) activity or anti-bacterial activity (Escherichia coli or Staphylococcus aureus). CONCLUSION: In contrast to experience with nonoxynol-9, PRO 2000 did not trigger an inflammatory response in cervicovaginal secretions. There was a modest reduction in mucosal immune mediators, but this loss was not associated with a reduction in intrinsic antimicrobial activity.

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4. PUBLISHED RESEARCH: RELEVANT BASIC AND TRANSLATIONAL SCIENCE

"Executive summary and recommendations from the WHO/UNAIDS/IAVI expert group consultation on 'Phase IIB-TOC trials as a novel strategy for evaluation of preventive HIV vaccines', 31 January-2 February 2006, IAVI, New York, USA"

Author(s): WHO/UNAIDS/IAVI International Expert Group

Reference: N/A 21(4):539-46.

Published Abstract: This report summarizes the discussions and recommendations from a consultation held in New York City, USA (31 January-2 February 2006) organized by the joint World Health Organization-United Nations Programme on HIV/AIDS HIV Vaccine Initiative and the International AIDS Vaccine Initiative. The consultation discussed issues related to the design and implementation of phase IIB 'test of concept' trials (phase IIB-TOC), also referred to as 'proof of concept' trials, in evaluating candidate HIV vaccines and their implications for future approval and licensure. The results of a single phase IIB-TOC trial would not be expected to provide sufficient evidence of safety or efficacy required for licensure. In many instances, phase IIB-TOC trials may be undertaken relatively early in development, before manufacturing processes and capacity are developed sufficiently to distribute the vaccine on a large scale. However, experts at this meeting considered the pressure that could arise, particularly in regions hardest hit by AIDS, if a phase IIB-TOC trial showed high levels of efficacy. The group largely agreed that full-scale phase III trials would still be necessary to demonstrate that the vaccine candidate was safe and effective, but emphasized that governments and organizations conducting trials should consider these issues in advance. The recommendations from this meeting should be helpful for all organizations involved in HIV vaccine trials, in particular for the national regulatory authorities in assessing the utility of phase IIB-TOC trials in the overall HIV vaccine research and development process.

5. POLITICS AND POLICY

"Bush signs FY 2007 \$463B spending bill that allocates \$1.3B increase to fund international HIV/AIDS, TB programs"

Date: 16 February 2007

Source: *Kaiser Daily HIV/AIDS Report*

http://www.kaisernetwork.org/Daily_reports/rep_hiv_recent_rep.cfm?dr_cat=1&show=yes&dr_DateTime=16-Feb-07#42980

President Bush on Thursday signed a \$463.5 billion spending resolution (HJ Res 20) for fiscal year 2007 that includes a \$1.3 billion increase for international HIV/AIDS and tuberculosis programs, the AP/Fox News reports (AP/Fox News , 2/15). The resolution brings the total for the President's Emergency Plan for AIDS Relief to \$4.5 billion. The \$4.5 billion for PEPFAR includes \$3.2 billion for the State Department's Global HIV/AIDS Initiative, \$712 million for USAID's Child Survival and Health Program, and \$494 million for CDC and HHS global HIV/AIDS activities. Of these amounts, \$724 million from PEPFAR is allocated for the U.S. contribution to the Global Fund To Fight AIDS, Tuberculosis and Malaria, with \$625 million coming from the State Department and USAID and \$99 million from HHS. In addition to the PEPFAR funding, \$248 million is allocated to expand programs under the President's Malaria Initiative, an increase of \$149 million. The resolution also allocates an additional \$75.8 million in funding for the Ryan White CARE Act, which provides care and services to people living with HIV/AIDS in the U.S., to bring its funding to \$1.2 billion. The Senate on Wednesday passed the resolution (*Kaiser Daily HIV/AIDS Report*, 2/15).

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6. ANNOUNCEMENTS

HIV Prevention Research: A Comprehensive Timeline

<http://avac.org/timeline-website/index.htm>

The AIDS Vaccine Advocacy Coalition (AVAC) has developed a new web-based tool to facilitate the process of understanding and making connections between developments in different areas of HIV prevention research, and developing a shared approach to broader AIDS prevention research advocacy. The webpage, "HIV Prevention Research: A Comprehensive Timeline" includes a timeline featuring key information on many of the major prevention trials that are currently underway. The timeline is designed to give a "big picture" of the overall AIDS prevention research field, and to help advocates gain familiarity with the purpose, timeframe and geographic location of studies looking at multiple different types of strategies. The timeline can be accessed at <http://avac.org/timeline-website/index.htm>

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