ALLIANCE FOR MICROBICIDE DEVELOPMENT

09 March 2007, Volume 8, Number 9

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!

Areas covered in this News Digest:

1. MEDIA COVERAGE OF MICROBICIDES

"Fair trials: If clinical research is to flourish, trials must be scrupulously ethical"
Date: 06 March 2007
Source: *The Guardian*
Author(s): Linda Nordling

http://education.guardian.co.uk/egweekly/story/0,,2026877,00.html

Human guinea pigs testing ineffective or even harmful drugs and money-grabbing drug companies riding roughshod over the poor; no, it's not a synopsis for The Constant Gardener 2, but the supposed roll-call for a controversy that has taken South Africa by storm.

On January 31, the US organisation Conrad announced the premature closure of a clinical trial of a **vaginal gel** to combat HIV/Aids. The reason the testing of cellulose sulfate stopped was that preliminary results indicated its use could lead to an increased risk of HIV infection. The results were unexpected as 11 earlier safety studies of the compound had identified no safety concerns.

Journalists painted a picture of scandal and injustice. One Sunday newspaper described the participants in the trial as "guinea pigs" and hurled allegations of misconduct at the researchers. In response, the country's medical research council put out a statement saying that all its trials go through rigorous ethical testing. The head of the organisation, Anthony Mbewu, told MPs at a parliamentary hearing on February 20: "There is a misconception that trials are undertaken to satisfy scientific curiosity or for money." However, he did call for the country's ethical review systems to be bolstered.

The health minister, Manto Tshabalala-Msimang, has ordered an inquiry into the case. This seems a prudent move, if a little tarnished by Tshabalala-Msimang's track record on HIV/Aids. She notoriously defended a move to showcase vegetables, including garlic and beetroot, side-by-side with clinically proven anti-HIV drugs at the international Aids conference in Toronto last August.

But even if her inquiry finds no evidence of wrongdoing or neglect, the future of HIV/Aids gel trials in the country hangs in the balance. There is a myth surrounding these treatments, says the Treatment Action Campaign. "The myth is that participants in **microbicide** trials (as well as vaccine trials and the recently conducted circumcision trials) are encouraged to have unprotected sex or, in the myth's most extreme version, exposed to HIV by researchers." Naturally, such myths need to be dispelled for new medicines to be developed and tested in South Africa, something hailed by the government as a way of attracting inward investment. But healthy scepticism should not be abandoned. An understanding needs to be built - not just in South Africa but all over the world - that while science outcomes can do untold good, science in itself is just a tool, which has the potential both to help and harm depending on the hands that guide it.

"Scientists discover 'natural barrier' to HIV"
Date: 05 March 2007
Source: *HealthDay News*
Author(s): E.J. Mundell

http://fe30.news.re3.yahoo.com/s/hsn/20070305/hl_hsn/scientistsdiscovernaturalbarriertohiv

Researchers have discovered that cells in the mucosal lining of human genitalia produce a protein that "eats up" invading HIV -- possibly keeping the spread of the AIDS more contained than it might otherwise be. Even more important, enhancing the activity of this protein, called Langerin, could be a potent new way to curtail the transmission of the virus that causes AIDS, the Dutch scientists added.

Langerin is produced by Langerhans cells, which form a web-like network in skin and mucosa. This network is one of the first structures HIV confronts as it attempts to infect its host. However, "we observed that Langerin is able to scavenge viruses from the surrounding environment, thereby preventing infection," said lead researcher Teunis Geijtenbeek, an immunologist researcher at Vrije University Medical Center in Amsterdam. "And since generally all tissues on the outside of our bodies have Langerhans cells, we think that the human body is equipped with an antiviral defense mechanism, destroying incoming viruses," Geijtenbeek said.

The finding, reported in the March 4 online issue of *Nature Medicine*, "is very interesting and unexpected," said Dr. Jeffrey Laurence, director of the Laboratory for AIDS Virus Research at the Weill Cornell Medical College, in New

York City. "It may explain part of the relative inefficiency of HIV in being transmitted."

Even though HIV has killed an estimated 22 million people since it was first recognized more than 25 years ago, it is actually not very good at infecting humans, relatively speaking. For example, the human papillomavirus (HPV), which causes cervical cancer, is nearly 100 percent infectious, Laurence noted. That means that every encounter with the sexually transmitted virus will end in infection. "On the other hand, during one episode of penile-vaginal intercourse with an HIV-infected partner, the chance that you are going to get HIV is somewhere between one in 100 and one in 200," Laurence said.

Experts have long puzzled why HIV is relatively tough to contract, compared to other pathogens. The Dutch study, conducted in the laboratory using Langerhans cells from 13 human donors, may explain why. When HIV comes in contact with genital mucosa, its ultimate target -- the cells it seeks to hijack and destroy -- are immune system T-cells. But T-cells are relatively far away (in lymph tissues), so HIV uses nearby Langerhans cells as "vehicles" to migrate to T-cells. For decades, the common wisdom was that HIV easily enters and infects Langerhans cells. Geijtenbeek's team has now cast doubt on that notion.

Looking closely at the interaction of HIV and Langerhans cells, they found that the cells "do not become infected by HIV-1, because the cells have the protein Langerin on their cell surface," Geijtenbeek said. "Langerin captures HIV-1 very efficiently, and this Langerin-bound HIV-1 is taken up (a bit like eating) by the Langerhans cells and destroyed." In essence, Geijtenbeek said, "Langerhans cells act more like a virus vacuum cleaner." Only in certain circumstances -- such as when levels of invading HIV are very high, or if Langerin activity is particularly weak -- are Langerhans cells overwhelmed by the virus and infected.

The finding is exciting for many reasons, not the least of which is its potential for HIV prevention, Geijtenbeek said. "We are currently investigating whether we can enhance Langerin function by increasing the amount of Langerin on the cell surface of Langerhans cells," he said. "This might be a real possibility, but it will take time. I am also confident that other researchers will now also start exploring this possibility."

The discovery might also help explain differences in vulnerability to HIV infection among people. "It is known that the Langerin gene is different in some individuals," Geijtenbeek noted. "These differences could affect the function of Langerin. Thus, Langerhans cells with a less functional Langerin might be more susceptible to HIV-1, and these individuals are more prone to infection. We are currently investigating this."

The finding should also impact the race to find topical **microbicides** that might protect women against HIV infection. Choosing compounds that allow Langerin to continue to work its magic will enhance any candidate **microbicide**'s effectiveness, the Dutch researcher said. Laurence did offer one note of caution, however. "In the test tube, this is a very important finding," he said. "But there are many things in the test tube that don't occur when you get into an animal or a human. Having said that, though, this is a very intriguing finding."

"Newly infected spread half of HIV"
Date: 02 March 2007
Source: *Globe and Mail (Canada)*
Author(s): Lisa Priest

http://www.theglobeandmail.com/servlet/story/LAC.20070302.HIV02/TPStory/?query=Newly+infected+spread+half+of+HIV%3B+

Half of all new HIV transmissions occur when people are unlikely to know they carry the virus and in some cases, wouldn't test positive for it because they are so newly infected, a Canadian study says. The study, to be published in the April edition of the *Journal of Infectious Diseases*, is one of the first in the world to quantify how many of the newly infected are responsible for spreading the disease to others.

And it raises troubling questions about how to deal with the problem: How can those at high risk be encouraged to come forward and undergo frequent, repeated tests when no one knows who they are? And should those at very high risk of contracting the disease be put on anti-retroviral therapy as a preventive measure? "From the standpoint of public health, we have a major problem in Canada and North America," study author Mark Wainberg, director of the McGill University AIDS Centre at the Jewish General Hospital, said in a telephone interview yesterday. ". . . One of the things driving this entire epidemic is that people themselves are newly infected and are often the most infectious they will ever be throughout their lives and often not even know it."

Those who have just become infected with HIV are at their most infectious as the virus madly replicates, making millions of copies. The immune system responds by launching a battle on the virus and making antibodies. Those going through this process, medically referred to as seroconversion, report flu-like symptoms, including fever and chills. Others, however, feel no differently. Most people, after being exposed to the virus, would test positive for it two to four weeks later; others may not test positive for the virus that causes AIDS until three and as long as six months later, said Rita Shahin, associate medical officer of health with Toronto Public Health.

"This is an important study," said Dr. Shahin, who was not involved in the research. "We've always known that people who don't know their HIV status are accounting for a significant percentage of transmissions. This further narrows it down to that group who are within the first six months of infection." She recommended testing of high-risk individuals every three to six months. Other efforts have included putting condoms in bathhouses, counselling and education.

Dr. Wainberg said those who learn of being HIV positive often modify their behaviour so as not to put others at risk. But modifying behaviour is not necessarily an option when someone does not even know or suspect they have the disease. At the end of 2005, an estimated 58,000 people in Canada were living with HIV infection, including AIDS. This represents an increase of about 16 per cent from the 2002 estimate of 50,000. Of those, 27 per cent would be unaware of their infection, according to Public Health Agency of Canada figures.

An accompanying editorial to the journal article, also posted online, stated it is time to evaluate the most potent intervention to treat the disease -- highly active anti-retroviral therapy -- as a form of prevention. "HAART is no replacement for enhanced behavioural approaches to reduce transmission," the editorial says. "It is expensive, and relatively toxic, and many regions of the world still have not implemented therapy to many of their infected populations. However, we argue that the current focus on increasing HIV diagnoses through more widespread testing requires a parallel strategy for minimizing ongoing transmission."

However, the editorial goes on to say "it is now time to evaluate application of the most potent intervention to treat this disease -- namely, an anti-retroviral therapy -- to its prevention." Dr. Wainberg agreed with the sentiment, saying that

there are clinical trials under way to determine whether the drugs to treat the disease can be used to prevent transmission among very high-risk groups, such as sex workers in the developing world. "We know through a study that came out a month ago that **microbicides** are not yet ready for prime time," he said in a telephone interview from Los Angeles, where he was attending a conference. "A related concept is giving them drugs orally as preventives." He also recommended that public-health officials try to identify high-risk people and encourage them to be tested, as well as providing more rapid testing.

"Studies find blind spots in African AIDS prevention: sexual culture, focus on drug distribution lend to HIV's spread"
Date: 02 March 2007
Source: *Washington Post*
Author(s): Craig Timberg

http://www.washingtonpost.com/wp-dyn/content/discussion/2007/02/16/DI2007021601817.html?nav=hcmodule

In relatively prosperous Botswana, a fourth of adults have AIDS--among women in Francistown in their early 30s, the rate is 69 percent.

Post Johannesburg Bureau Chief Craig Timberg was online Friday, March 2 at 1 p.m. ET take questions on his article on faltering anti-AIDS efforts in southern Africa, where a permissive sexual culture and a focus on providing free medicine appear to be helping the disease spread.

The transcript follows (*EDITORS' NOTE: Due to the length of this transcript, we have included only those portions specifically relevant to **microbicides**):*

...Washington: Hi Craig. I just returned from Durban, South Africa, and attended a community meeting regarding the urgent need for a variety of HIV prevention options, including **microbicides**. My first question is, why so you think more leaders encourage a no-grazing policy, like in Uganda?

Craig Timberg: I think the Western world and its big donors have gotten very fixated on the possibility of big-dollar high-tech fixes such as **microbicides** and vaccines, while neglecting things that (while uncomfortable to talk about like modifying sexual behavior) have shown some track record of working...

...Washington: Obviously, married couples are not going to suddenly abstain, and married women in Africa (or anywhere, for that matter) can't demand that their husbands use condoms. This is why **microbicides**, in a variety of forms, are crucial. You refer to **microbicides** and vaccines as high-tech, high-dollar solutions, but don't you think investment in both is necessary in addition to behavioral changes?

Craig Timberg: Um, that's a tough one. I think a **microbicide** would be a very valuable thing if the scientific dilemmas can be sorted out, but if you don't believe women can demand condoms (some clearly can, by the way), then are they going to be able to interrupt their husband/boyfriend/etc. to take a moment in the bathroom and insert a gel? we don't know the answer to that question yet. Lots of things that look good on paper haven't slowed the spread of HIV to a meaningful extent.

As for a vaccine, yes, it would be great. But the vaccines they are talking about would be, at best, maybe 50 percent effective - which is less effective than circumcision (a readily available technology, though clearly a more intrusive one) at preventing HIV....

"HIV drugs to be evaluated"
Date: 01 March 2007
Source: *The Daily Record (Baltimore, MD)*

ImQuest Pharmaceuticals Inc., of Frederick, which develops novel drugs to treat infectious diseases and cancer, announced it was awarded a grant by the **International Partnership for Microbicides** to conduct preclinical evaluation of the topical use of pyrimidinediones, a class of drugs that are used to inhibit the transmission of HIV in women. **Microbicides** are compounds that can be applied inside the vagina or rectum to protect against sexually transmitted infections, including HIV, according to the World Health Organization's Web site.

"New drug stirs scientists' hopes of halting AIDS"
Date: 01 March 2007
Source: *The Star-Ledger*
Author(s): Kitta MacPherson

http://www.nj.com/news/ledger/index.ssf?/base/news-11/117273007974610.xml&coll=1

An experimental AIDS drug, years in the making by scientists from Johnson & Johnson and Rutgers University, is part of an assortment of startlingly effective new treatments shown to zap resistant strains of HIV. Scientists from J&J's Tibotec division reported the results yesterday at the end of a major AIDS conference in Los Angeles. The drug, TMC-278, has long been viewed as the most promising of a family of revolutionary AIDS compounds called "DAPY" (rhymes with "happy') being developed by the New Brunswick drug giant.

"Right now, it looks as if this could be a home run for patients," said Roger Pomerantz, president of J&J's Tibotec Pharma Ltd. in Yardley, Pa., minutes after a presentation before a standing-room-only crowd of 4,000. "I am very jazzed about this. It's going to have a huge impact."

The J&J AIDS presentation followed a equally riveting talk by scientists from Gilead Sciences Inc. in California on their treatment advances, as well as announcements on Tuesday by Merck & Co. of Whitehouse and Pfizer of New York of major strides in AIDS treatment. All of the new drugs attack difficult-to-treat "resistant" strains of the virus and that news has energized the AIDS community.

"It's a brand-new day," said Stephen Smith, a physician-scientist who directs the department of infectious disease at Saint Michael's Medical Center in Newark. "This means that no one in the developed world should be walking around anymore with any detectable levels of virus in their blood. These drugs are just blowing me away."

The announcements made at the *14th annual Conference on Retroviruses and Opportunistic Infections*, according to Smith and other experts, are as revolutionary as the breakthroughs of the mid-1990s when scientists developed drug

cocktails to stop AIDS.

Merck's drug, MK-0518, blocks an enzyme called integrase that helps the virus replicate. The company plans to seek federal approval before July 1 to use the drug against resistant HIV, the deadly virus that causes AIDS. Gilead also presented promising results from tests on its integrase inhibitor, GS-9137, which is in second-stage testing.

Pfizer's HIV pill, named maraviroc, is the first of a new class of medicines called CCR5 inhibitors that block a chemical doorway used by the virus to infect cells. A chemical cocktail that included maraviroc suppressed the drug in patients who do not respond to older treatments, scientists reported.

Resistant strains, caused when the quick-change artist that is HIV morphs its shape and structure to survive lethal drug attacks, is a huge and growing medical problem. About 10 percent of new HIV patients are infected with a virus resistant to at least one type of AIDS drug, according to a study released earlier this week by the federal Centers for Disease Control and Prevention in Atlanta. And five people in 1,000, according to the study, suffer from a form that evades all three major AIDS therapies currently available.

TMC-278 ("Tibotec medical compound") is a non-nucleoside reverse transcriptase inhibitor. Like other drugs in this category, it jams the machinery of reverse transcriptase, one of the prime proteins responsible for the reproduction of HIV. But 278 is a DAPY compound, so it is special, according to its designers. So named because they have diarylpyrimidine at their core, these drugs are made of flexible molecules that find ways to fit into portals on the surface of proteins, like a master key adjusting to many locks. "This drug sort of bobs and weaves, if you will, and stays in the pocket," said Pomerantz of Tibotec. In data presented at the conference, Tibotec scientists said the drug was as effective at lowering HIV levels in newly diagnosed patients as Bristol-Myers Squibb's popular Sustiva.

Anton Pozniak, managing director of St. Stephen's AIDS Trust in London, who led the study, said drug combinations that included TMC-278 at three different dose levels lowered the amount of HIV as much as standard doses of Sustiva used in similar combinations. The drug can be easily combined with others to form a single pill, company officials said, and causes fewer side effects than others on the market. In addition, the drug appears to be non-toxic to pregnant women and their fetuses, which could be an enormous benefit in the developing world where so many of the newly infected patients are women.

Two other Tibotec drugs, also DAPY compounds, are making steady progress, Pomerantz said. TMC-125, which does not combine as well into a single pill but is potent against the virus, has moved through clinical trials and is close to FDA approval. TMC-120 is being studied for its use as a **microbicide** (an AIDS cream) and has passed initial safety tests, he said.

Research teams at the Center for Advanced Biotechnology and Medicine on Rutgers' Busch campus have studied reverse transcriptase as well as the DAPY compounds for more than a decade. Over the past year, Rutgers researcher Joseph Bauman created a detailed image of TMC-278 through crystallography, technology that reveals the atomic structures of compounds. He then interlocked TMC-278 with reverse transcriptase, an advance expected to lead to new drugs made from DAPY compounds. "Any time that basic science can lead to new, ideal options for patients with dreadful disease, that's a triumph of enormous magnitude," said Eddy Arnold of Rutgers University, an AIDS expert who supervised Bauman and has long investigated the intricacies of reverse transcriptase.

"Exploring the potential of HIV microbicides"

Source: *NCRR Reporter, Winter 2007, Vol. 31, No. 1*

http://www.ncrr.nih.gov/newspub/Winter07rpt/stories1.asp

The face of the AIDS epidemic has changed considerably in the last quarter of a century. Although the disease was first identified in homosexual men, today women comprise half of the world's nearly 40 million HIV-infected individuals. Most of these women became infected through heterosexual contact.

Women are particularly vulnerable to HIV infection, because their mucosal exposure to the virus during intercourse is greater than men's. Condoms can help prevent HIV transmission, but their use is not under a woman's control. Because of these and other vulnerabilities, new HIV infections now arise more rapidly among women than among men in many parts of the world.

Public health officials have long called for new HIV prevention methods for women--methods that are inexpensive, easy-to-deliver, and under their control. This need is especially urgent, given that a cure for AIDS and development of a safe and effective HIV vaccine has proven elusive.

Microbicides are substances, typically formulated as gels or creams, that can be applied topically to the vagina to prevent sexual transmission of HIV or other pathogens. The products, now being tested in preclinical and clinical studies, may offer women the protection they need. Mathematical models predict that if only 20 percent of women in the developing world used a **microbicide** in just half of their sexual encounters, 2.5 million HIV infections could be prevented over a three-year period.

NCRR-funded resource centers are helping scientists to pursue novel approaches to **microbicides** on several fronts. Investigators supported by NCRR's Research Centers in Minority Institutions (RCMI) Program are conducting preclinical studies of an effective yet inexpensive **microbicide** based on a common product additive. An NCRR-supported General Clinical Research Center (GCRC) is helping efforts to examine both how **microbicides** react to the human vaginal environment and how the vagina reacts to the compounds. And studies with macaque monkeys at the NCRR's National Primate Research Centers (NPRCs) are uncovering new roles for **microbicides** and developing approaches that target the molecular interactions between HIV and the immune cells it invades.

In the 1980s, scientists working at NCRR-funded NPRCs laid the groundwork for much of today's HIV research when they discovered the simian immunodeficiency virus (SIV), a close relative of HIV that infects nonhuman primates. SIV infection in macaque monkeys has since become a vital animal model for the study of HIV infection, treatment, and prevention.

Soon after the discovery of SIV, Christopher Miller, a researcher at the California NPRC at the University of California, Davis, and his colleagues showed that they could infect monkeys in a way that mimics sexual transmission of HIV in humans by applying SIV to the genital mucous membranes of macaques. Studies with these monkeys have shown how SIV spreads systemically from genital mucosal sites. "This is a particularly good model for understanding what happens in human HIV infections, because these nonhuman primates have the same sort of anatomy and physiology as do humans, and they also have 28-day menstrual cycles, just as women do," says Miller. "Especially for studies

that hopefully will be predictive of how an intervention affects human patients, we want the animal model to be as close as possible to the real thing."

Miller and his colleagues recently found that new SIV infections in female macaques remain limited for about four days to a relatively small number of cells, primarily in the vagina and cervix. "There's something of a delay between the time that the virus comes in contact with the genital tract and the time that full-fledged systemic replication of the virus occurs," says Miller. This finding suggests that **microbicides** might do more than just block sexual transmission of HIV. If a woman has already become infected through sexual contact, a **microbicide**, if administered soon enough, might prevent or limit a wider systemic HIV infection. "It gives people hope and a rational basis to keep exploring interventions that are aimed at an early timepoint," he says.

At the Tulane NPRC, another NCRR-funded primate center, Ronald Veazey and his colleagues are testing a promising new type of **microbicide** called a fusion inhibitor. These agents inhibit infection in a specific and targeted way by preventing the binding, or fusion, between glycoprotein molecules on the outer coat of HIV particles and the receptors for those glycoproteins on the surface of immune cells.

Veazey studies fusion inhibitors that target a type of cellular receptor called CCR5. As one of the main receptors that HIV uses to infect cells, CCR5 appears to play a major role in HIV transmission across mucosal surfaces, like those in the vagina. When these fusion inhibitors bind to a cell's CCR5 receptors, they block viral access to the receptors and in some cases also trigger cellular changes that reduce the number of receptors on the cell's surface. These mechanisms greatly limit viral entry points into the cell.

Veazey and his colleagues have found that both vaginal and oral administration of CCR5-based fusion inhibitors protects macaques against infection. "We've shown tremendous proof of concepts in blocking this receptor," says Veazey. "Blocking CCR5 seems to be all that is necessary to prevent transmission of the AIDS virus, at least in the monkey model."

In one study, the researchers administered three experimental **microbicide** gels, alone and in combination, to female macaques and found that all three were protective against vaginal infection with simian HIV. In addition, significant protection was achieved when two of the agents--known as Compound 167 and BMS-378806--were administered in combination. The combination gel was protective, even when applied up to six hours before viral exposure. In a separate study, Veazey and colleagues found that orally administered formulations of Compound 167 can prevent vaginal infections of simian HIV in macaques.

Scientists are now working to develop more cost-effective molecular preparations of fusion inhibitors. "Clearly, the CCR5 point of attack is extremely effective. Our major obstacle now is to develop a fusion inhibitor that can be produced economically," says Veazey. Clinical trials of the fusion inhibitor gels are now being planned.

Another novel approach to **microbicide** development is being pursued in preclinical studies at the NCRR-funded RCMI at Meharry Medical College in Nashville. James Hildreth, director of Meharry's Center for AIDS Health Disparities Research, is investigating an agent called beta-cyclodextrin. Cyclodextrins are simple polymer sugars that are already widely used in a variety of products, including mouthwash, topical creams, food flavorings, and some intravenous medications. "Cyclodextrin is easy to synthesize, very inexpensive to produce, and if it works it will cost about 7 cents per application," says Hildreth. "For developing countries, where the annual income is often only a few hundred dollars per year, we have to produce something that is very inexpensive."

In 2001, when Hildreth was an associate professor at Johns Hopkins University School of Medicine, he and his colleagues discovered that cholesterol plays a critical role in HIV fusion and entry into cells. In later studies, the scientists showed that HIV buds from infected cells at cholesterol-rich regions known as lipid rafts, small fatty globules scattered throughout cellular membranes. "HIV is a thief. It steals proteins and other molecules from the host cell when it buds from that cell," says Hildreth. "In 2003 we showed that HIV particles themselves also appear to have lipid rafts, probably picked up from cellular membranes as the virus exits the cell."

Further studies revealed that beta-cyclodextrin drains cholesterol from both HIV and the host cell membrane. "As you remove cholesterol from HIV particles, you can unplug that lipid raft, and the virus will lose its essential components and become noninfectious," Hildreth says. The compound also enables healthy cells to resist HIV and makes infected cells less able to spread the virus.

By studying mice that contain transplanted human cells, Hildreth and his colleagues demonstrated that beta-cyclodextrin can prevent cell-to-cell transfer of HIV, an important route of infection for sexually transmitted virus. In 24 out of 27 mice, vaginal administration of beta-cyclodextrin blocked the passage of HIV from infected cells in the vagina to uninfected cells in the body.

Encouraged by his mouse research, Hildreth is planning a small clinical trial at Meharry's RCMI Clinical Research Center to assess the safety of a beta-cyclodextrin **microbicide** in women. Beta-cyclodextrin has already been found safe for human use in toxicity studies related to its various product applications.

Some **microbicide** candidates have already advanced to clinical trials, although these generally have a less specific and targeted mechanism of action than the CCR5 fusion inhibitors and other agents now being investigated in preclinical studies involving animals. Among the compounds currently in clinical trials, substances called sulfated polyanions, which bind proteins HIV uses to enter human cells, appear particularly promising. The National Institute of Allergy and Infectious Diseases is currently funding a multicenter clinical trial--involving more than 3,000 women in the United States and Africa--examining both a sulfated polyanion called PRO 2000/5 and a gel designed to lower the pH of the vagina (BufferGel) to evaluate their safety and ability to prevent HIV infection in at-risk women. Other NIH-funded **microbicide** clinical trials are also under way.

Along with their colleagues, Marla Keller and Betsy Herold at the NCRR-supported GCRC at Mount Sinai School of Medicine in New York recently showed that the environment of the human vagina does not lessen the potency of PRO 2000/5. In fact, they demonstrated for the first time that a **microbicide** can remain highly effective after contact with the human vagina.

The researchers placed PRO 2000/5 into the vaginas of 10 women and then collected cervicovaginal fluid samples. The samples were mixed independently with HIV and herpes simplex virus type 2 (HSV-2)--the pathogen responsible for genital herpes, which is known to increase a person's risk for HIV. When human cells were inoculated with the cervicovaginal samples, the PRO 2000/5, still present in the samples, inhibited both HIV and HSV infection at least 1,000-fold. In a follow-up study, involving 24 healthy women, Herold and Keller determined that daily applications of PRO 2000/5 does not trigger an inflammatory response in cervicovaginal secretions, suggesting that repeated use of this **microbicide** is safe.

By supporting this type of clinical research, as well as preclinical animal-based studies, NCRR is helping to translate basic research findings into potential AIDS-prevention strategies for women. While NCRR's nonhuman primate

resources are helping to identify and evaluate promising **microbicides**, the RCMI and patient-oriented resources stand ready to facilitate clinical investigations. Through these efforts, NCRR is assisting NIH's broad efforts to provide women with an effective agent that they can easily and safely use to achieve protection from HIV infection.

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2. PUBLISHED RESEARCH: MICROBICIDE-SPECIFIC

"Awareness and attitudes regarding microbicides and nonoxynol-9 use in a probability sample of gay men"
Author(s): Carballo-Dieguez A, O'sullivan LF, Lin P, et al
Reference: N/A 11(2):271-6.

Published Abstract: A household probability sample of 879 adult gay and other men who have sex with men in San Francisco underwent phone interviews. Approximately, half reported recent unprotected anal intercourse (UAI). Yet, lubricant use was high, a behavior that may facilitate future adoption of topical **microbicide** delivered by a lubricant gel. Despite warnings against Nonoxynol-9 (N-9), 26% of respondents reported still using it. **Microbicide** awareness was higher among men reporting UAI than among consistent condom users. Scenarios presenting **microbicides** "as effective as condoms," "nearly as effective," or "less effective but better than nothing" produced wide variability in willingness to use them, which may have implications for **microbicide** acceptability. HIV-infected men and those who reported UAI showed greater **microbicide** acceptance.

"Biophysical analysis of prototype microbicidal gels"
Author(s): Owen DH, Peters JJ, Kieweg SL, et al
Reference: N/A 96(3):661-9.

Published Abstract: The objective of this study was to evaluate the distribution and retention (deployment) of four prototype vehicles for delivery of prophylactic **microbicides** against vaginal HIV transmission. Study gels were created with different molecular compositions, producing different biophysical properties governing vaginal deployment. The study employed three techniques: direct rheological measurement of gel properties, direct observation of gel surface coating erosion, and dissolution by a vaginal fluid simulant, and mathematical modeling of gel squeezing flow processes. Results suggest significant differences in extent of vaginal coating after gel application and in erosion of these gel layers due to contact with ambient vaginal fluid and shearing. The relationships between gel rheological properties, coating flow and erosion of coating were not always anticipated from differences in gel molecular composition.

"Interpreting properties of microbicide drug delivery gels: analyzing deployment kinetics due to squeezing"
Author(s): Kieweg SL, Katz DF
Reference: N/A 96(4):835-50.

Published Abstract: Prophylactic efficacy of topical **microbicidal** drug delivery formulations against HIV may depend upon their abilities to coat and be retained on epithelial surfaces where infection begins. Rheological and surface properties play paramount roles in governing coating. While fundamental fluid mechanical studies of epithelial coating mechanisms have begun, their results have not previously addressed questions of practical value to formulators in the pharmaceutics community. The present theoretical study began this process. We focused upon squeezing flows of seven **vaginal gels** which are models for future **microbicides** or a candidate formulation in clinical trials. Each formulation is based upon one of three different macromolecules: cellulose, polyacrylic acid (PAA), or carrageenan. We addressed: (1) properties with greatest influence on squeezing flow; (2) alterations of properties to improve measures of coating dynamics; and (3) effects of polymer concentration and temperature on coating dynamics. We found that yield stresses dominated flows of PAA gels, and that surface slip, while small, significantly influenced coating by cellulose gels. Decreases in consistency, increases in shear-thinning, and increases in temperature led to thinner coatings. Details of altered coating rates depended upon parameter values and time. Specific polymer concentration effects differed between cellulose and PAA gels, though trends were similar.

"The promise of CCR5 antagonists as new therapies for HIV-1"
Author(s): Repik A, Richards KH, Clapham PR
Reference: N/A 8(2):130-9.

Published Abstract: The chemokine receptors CCR5 and CXCR4 were identified as HIV-1 co-receptors in 1996. Since then, a range of agents that bind these receptors and potently block HIV-1 infection have been described, including monoclonal antibodies, peptides and modified chemokines. However, small organic molecules that bind CCR5 are currently the most promising of the co-receptor antagonists for the potential treatment of HIV. These agents are now in advanced stages of clinical development and should soon augment current therapies, as well as being candidates for inclusion in **microbicides**. Unlike existing drugs that target HIV proteins (eg, reverse transcriptase and protease), co-receptor antagonists bind receptors encoded by the host. As a consequence, blockade of these receptors may result in immunosuppressive effects or other disorders. Furthermore, co-receptor inhibitors may also be more toxic than currently available HIV therapies, and it is not yet clear whether they will become candidates for first-line therapy. Nonetheless, safer, less toxic versions of such inhibitors may be achievable in the future. The use of CCR5 inhibitors as a second-line treatment increases the possibility that these reagents will select for more pathogenic CXCR4-using variants. The development of effective CXCR4 antagonists for dual treatment would be beneficial; however, whether long-term treatment with antagonists of the widely expressed CXCR4 receptor is feasible without toxicity is unknown. This review discusses the current status of CCR5 antagonists, their modes of action and their development for therapeutic use.

"The retrocyclin analogue RC-101 prevents human immunodeficiency virus type 1 infection of a model human cervicovaginal tissue construct"
Author(s): Cole AL, Herasimtschuk A, Gupta P, et al
Reference: N/A Epub ahead of print.

Published Abstract: Retrocyclins are cyclic antimicrobial peptides that exhibit potent activity towards a broad range of primary and laboratory-adapted strains of human immunodeficiency virus type 1 (HIV-1) *in vitro*. The current study shows that RC-101, an analogue of retrocyclin, prevented HIV-1 infection in an organ-like construct of human cervicovaginal tissue and retained full activity in the presence of vaginal fluid. The peptide remained within the cervicovaginal tissues throughout the 9-day incubation period without altering tissue viability, inducing damage or inducing the release of inflammatory cytokines. Collectively, these data support the potential development of RC-101 as a topical **microbicide** to prevent HIV-1 infection and transmission.

"The utility of non-proportional quota sampling for recruiting at-risk women for microbicide research"
Author(s): Morrow KM, Vargas S, Rosen RK, et al
Reference: N/A Epub ahead of print.

Published Abstract: In the context of a measurement development study designed to contextualize **microbicide** acceptability, a sample that represented a range of at-risk women and maintained the statistical power needed for validity analyses was required. A non-proportional quota sampling strategy focused on race/ethnicity and number of sexual partners was utilized. This strategy resulted in enrollment of approximately equal proportions of Latina (31%), Black (36%), and White (32%) women, and an approximately 1:2 ratio of single-partnered (29%) and multi-partnered (71%) women. About 17% of women screened were ineligible based on eligibility criteria; an additional 16% were ineligible based on quota closures. Most participants were recruited through word of mouth (39%), community-based organizations (19%), or media sources (19%). Women recruited through word of mouth had the highest screen-to-interview completion percentage (67%). Non-proportional quota sampling is a feasible option for ensuring adequate representation of sample characteristics in **microbicide** research, but this goal should be weighed against cost and staff burden.

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3. PUBLISHED RESEARCH: RELEVANT BASIC AND TRANSLATIONAL SCIENCE

"Novel inhibitors of the early steps of the HIV-1 life cycle"
Author(s): Citterio P, Rusconi S
Reference: N/A 16(1):11-23.

Published Abstract: Considerable advances have been made on compounds that are active as inhibitors of HIV entry and fusion. The discovery of chemokines a few years ago focused the attention on coreceptor inhibitors in addition to fusion and attachment blockers. During the last 5 years, there has been an intense research activity from both private companies and academic institutions to find effective compounds that are capable of inhibiting the initial steps in the HIV life cycle. Some of the presented compounds demonstrated *in vitro* synergism, thus there is the rationale of their combined use in HIV-infected individuals. Many entry and fusion inhibitors of HIV are being

investigated in controlled clinical trials and there are a number of them that are bioavailable as oral formulations. This is an essential feature for an extended use of these compounds with the purpose of ameliorating patients' adherence to medications; therefore, preventing the development of drug resistance. Among the many compounds that are being investigated, some are in the preclinical arena and others are more advanced in development stages. Overall, the main aim is to establish the action of these compounds on the immune system (e.g., the balance of the system after shutting off CCR5 or CXCR4 coreceptors) and the possible burden of unexplained side effects. This review focuses on the recent developments in this field with a particular attention on promising compounds in preclinical and clinical trials.

"Overhauling clinical trials"
Author(s): Scott CT, Baker M
Reference: N/A 25(3):287-92.

Published Abstract: Designing clinical trials that adapt midstream is billed as a cure for drug development blues, one that can save time, money and improve patients' lives. Are these new designs safe and effective or an expensive gimmick?

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4. OTHER PREVENTION APPROACHES

"HIV study raises caution about circumcision"
Date: 07 March 2007
Source: *Washington Post*
Author(s): David Brown

http://www.washingtonpost.com/wp-dyn/content/article/2007/03/06/AR2007030601911.html

Men with HIV who get circumcised hoping they will be less likely to transmit the AIDS virus may have a greater-than-normal risk of infecting their partners if they resume sexual activity too soon after the operation. That observation -- drawn from preliminary analysis of a study in Uganda -- threatens to complicate efforts to tout circumcision as a new weapon against HIV in Africa. Specifically, it suggests that public health campaigns promoting circumcision must also include messages, directed principally at women, warning of the extreme hazard of intercourse with HIV-positive men who have just had the procedure.

The new data were presented yesterday to 75 government health ministers, scientists and policymakers from the World Health Organization and the U.N. AIDS program, and other experts meeting in Montreux, Switzerland, to develop guidance on using circumcision as a prevention measure. Three studies, including two published last month, show that circumcision lowers a man's risk of acquiring HIV infection by half -- protection roughly equivalent to a moderately effective vaccine. Researchers hope it might indirectly protect women as well. That could happen because circumcised men are less likely to have genital ulcers, which increase an infected person's risk of transmitting the

virus. More broadly, if circumcision reduces HIV prevalence in a whole population, both sexes will benefit.

"The data that we have heard do not derail [the potential usefulness of circumcision] by any means," said Kevin De Cock, director of the HIV/AIDS department at WHO. "What it does do is provide a little more insight about the complexities that face us."

The research covers the Rakai district of southern Uganda, which has been hard hit by the AIDS epidemic. The study is being run by Ugandan researchers and scientists at the Johns Hopkins Bloomberg School of Public Health. It involved about 1,000 HIV-infected men, half of whom were randomly assigned to undergo circumcision. The researchers looked at the experience of 124 couples in which the regular female partner was uninfected at the time the man had the procedure.

Among 70 men who were circumcised, 11 transmitted HIV to their partners. Of the 54 who were not circumcised, four passed on the infection. Almost all new transmissions occurred in the first six months. Because there were so few cases in either group, the findings were not statistically significant and may have occurred only by chance. Of 12 men who resumed sexual activity before a physician had "certified" them as healed, three transmitted the virus to a partner. Of 55 men who waited, six transmitted the virus. Healing takes about one month.

An independent panel of scientists overseeing the study recommended that no new volunteers be enrolled because, even though the early findings were not statistically significant, it concluded that the original hypothesis -- that uninfected women would indirectly benefit over the short term from male circumcision -- was unlikely to prove true.

Much remains unknown. For example, some infected women may have acquired HIV from someone other than their regular partner -- a possibility the researchers will now look into by doing genetic fingerprinting on both the men's and the women's viruses.

One leader of the study, Maria Wawer of Johns Hopkins, said that for the moment "the need for extreme precaution and abstinence from sex in the post-procedure period cannot be overemphasized."

David Serwadda, a public health physician at Uganda's Makerere University, said the demand for circumcision, in male infants and in adults, has risen noticeably in his country in recent months.

Ezekiel J. Emanuel, a bioethicist at the National Institutes of Health who has written about ethical issues of circumcision research, noted that "this is not the first public health measure that will require careful education of the population that is being targeted."

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5. POLITICS AND POLICY

"Advocates on International Women's Day highlight discrimination, need to end impunity for sexual violence"
Date: 08 March 2007
Source: *Kaiser Daily Womens Health Policy Report*

http://www.kaisernetwork.org/daily_reports/rep_women_recent_reports.cfm?dr_cat=2&show=yes&dr_DateTime=08-Mar-07#43440

Advocates worldwide on International Women's Day on Thursday highlighted issues such as gender equality, discrimination and the need for justice for survivors of sexual violence, Reuters reports (Nichols, Reuters, 3/7). United Nations Secretary-General Ban Ki-moon on Wednesday said that although world leaders reaffirmed the importance of gender equality in "almost all countries, women continue to be under-represented in decision-making positions." He also said that the majority of the more than 100 million children who are not in school are girls and that women's "work continues to be undervalued, underpaid or not paid at all." In addition, violence against women continues "in every continent, country and culture" because it is concealed or condoned, Ban said (*Zee News*, 3/7). The U.N. Development Fund for Women and UNICEF on Wednesday said that 104 countries in the world have made rape a crime, but these laws have been poorly enforced (Reuters, 3/7). World Health Organization Director-General Margaret Chan in a statement released Wednesday said one in five women reports being sexually abused before age 15, which is associated with poor health for years. In addition, more than half a million women die annually from complications related to pregnancy and childbirth, Chan added (Chan statement, 3/7). Rima Salah, deputy executive director of UNICEF, said, "Sexual violence is a weapon of war with the strategic intent to humiliate communities ... to really disintegrate the fabric of society," adding, "No one, including the U.N. itself, is doing enough to end this terrible situation. We fail to treat it as a crime" (Reuters, 3/7).

Actions Worldwide

Ban on Wednesday said he would "pledge to work for a collaborative and coordinated approach to gender perspectives -- one that involves and engages the entire U.N. system in supporting member states' work for gender equality and empowerment of women" (IANS/*Malaysia Sun*, 3/7). The U.N. Security Council on Wednesday called for an end to impunity for gender-based violence during armed conflict and the inclusion of sexual and other violent acts against women and girls in crimes against humanity, war crimes and genocide prosecutions (Reuters, 3/7). The reproductive rights group Ipas on Thursday is holding a seminar in Rosebank, South Africa, where leaders in the field of women's health will analyze progress made in the promotion of women's health, including abortion, in South Africa and on the continent, South Africa's *Mail and Guardian* reports (Van der Post, *Mail and Guardian*, 3/8). In Afghanistan, female members of parliament and officials met in the capital to promote the registration of marriages and to discuss steps to stop the practice of self-immolation (Agence France Presse, 3/8). In Toronto, the Royal Cinema on Thursday planned to show the North American premiere of the movie "Killer's Paradise," a joint production of the National Film Board and BBC that portrays violence against women in Guatemala (Walker, *Toronto Star*, 3/8).

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6. ANNOUNCEMENTS

5th European Congress on Tropical Medicine and International Health

www.trop-amsterdam2007.com

Abstracts are invited before 15 March 2007 for the 5th European Congress on Tropical Medicine and International Health, which will take place from 24-28 May in Amsterdam. The Congress is organized under the auspices of the Federation of the Societies of Tropical Medicine and International Health, and it will be held in the Netherlands to commemorate the 100th anniversary of the Dutch Society for Tropical Medicine and International Health (NVTG). The theme is *Partnership and Innovation in Global Health*.

For more information, visit www.trop-amsterdam2007.com

NFPRHA welcomes new CEO Mary Jane Gallagher

Mary Jane (MJ) Gallagher has been selected by the National Family Planning and Reproductive Health Association (NFPRHA) Board as the AssociationÃ¢â‚¬â„¢s new President and CEO, replacing Judith M. DeSarno, who led the organization for 15 years. MJ brings a wealth of managerial, political, and communications experience to the position. Her first official day at NFPRHA was February 20.

Most recently, she served as Chief Operating Officer (COO) for the Public Education Network in Washington, D.C. Prior to that, MJ served as the COO for the League of Conservation Voters from 2004-2006 and for NARAL from 2001-2004. She also has been the CEO of the Gallagher-Widmeyer Group, a for-profit firm that focused on public affairs, communications, and not-for-profit consulting. For over 15 years, GallagherÃ¢â‚¬â„¢s public affairs work focused on maternal and child health care for those living in poverty. Earlier in her career, MJ served as press secretary to former Governor Jay Rockefeller (WV), director of policy & communications for former Governor Lawton Chiles (FL), and as a national political reporter for the MacNeil-Lehrer NewsHour.

Ã¢â‚¬Å“The Board is pleased after a national search to bring MJ Gallagher in to lead our efforts to secure funding and enhance services for low-income Americans in need of family planning services. MJÃ¢â‚¬â„¢s experience with local, state and national policymakers will enable us to better serve our members who provide family planning services at over 4,000 clinics nationwide,Ã¢â‚¬Â said NFPRHA Board Chair Nancy Sasaki, of Planned Parenthood of San Diego and Riverside Counties.

Ã¢â‚¬Å“If we are to truly achieve our shared national goal of reducing the number of unintended pregnancies and the need for abortion in this country, then now is the time to redouble our collective efforts to support quality family planning services for all of those in need,Ã¢â‚¬Â added Gallagher.

Office of AIDS Research Advisory Council (OARAC) Meeting

The Office of AIDS Research Advisory Council has announced a meeting to take place April 19, 2007, from 9 a.m. to 5 p.m. at the National Institutes of Health, 5635 Fishers Lane, Rockville, MD 20852. The meeting will focus on HIV-related Complications including Malignancies, Cardiovascular Disease, and Metabolic Complications. An update will be provided on the OARAC Working Groups for Treatment and Prevention Guidelines. The meeting will be open to the public, with attendance limited to space available.

Contact Person: Christina Brackna, Coordinator, Program Planning and Analysis, Office of Aids Research, Office of the Director, NIH, 5635 Fishers Lane MSC 9310, Suite 4000, Rockville, MD 20852, (301) 402-8655, cm53v@nih.gov.

Additional information is available at http://www.oar.nih.gov/meetings/default.htm

PATH Vacancy: Microbicides Media and Communications Initiative Officer

http://www.path.org/job.php?id=2119

Title: **Microbicides** Media and Communication Initiative Officer (MMCI Officer)
Program area: Global Campaign for **Microbicides**
Location: Johannesburg, South Africa
Posted date: 2/23/07
Closing date: Open until filled
Official (grade) title: (5020/5030) Program Officer I/II
Starting annual salary range: Commensurate with experience within in PATH's salary structure.

Overview: The Global Campaign for **Microbicides** is an international coalition of non-governmental organizations and advocates working to accelerate access to safe and effective forms of HIV prevention, especially **microbicides**. Through advocacy, policy analysis, and social science research, the Campaign works to accelerate product development, facilitate widespread access and use, and protect the needs and interests of users.

For more information, visit: http://www.path.org/job.php?id=2119

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