



ALLIANCE FOR MICROBICIDE DEVELOPMENT

25 January 2008, Volume 9, Number 4

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

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

Its purpose is to:

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

The *News Digest* is produced in a web-based format. Readers can view complete issues of the Digest or search by keyword for individual articles at <http://www.microbicide.org/publications/>. If you would like to be removed from the *Digest* distribution list, please send an email to digest@microbicide.org. 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. ALLIANCE UPDATES AND COMMUNITY NEWS

- [Industrialization Symposium at Microbicides 2008](#)
- [Population Council's Anticipated Carraguard Timeline](#)

2. MEDIA COVERAGE OF MICROBICIDES

- [Virology: the battle within](#)
- [Time for microbicide development](#)

3. PUBLISHED RESEARCH: MICROBICIDE-SPECIFIC

- [Acceptability of microbicidal surrogates among Zambian women](#)
- [Preclinical evaluation of lime juice as a topical microbicide candidate](#)
- [Sexual coercion and sexual desire: ambivalent meanings of heterosexual anal sex in Soweto, South Africa](#)

4. PUBLISHED RESEARCH: RELEVANT BASIC AND TRANSLATIONAL SCIENCE

- Herpes simplex virus type 2 acquisition during recent HIV infection does not influence plasma HIV levels
- Inhibition of HIV-1 infectivity through an innate mechanism involving naturally occurring IgM anti-leukocyte autoantibodies
- The association between school attendance, HIV infection and sexual behaviour among young people in rural South Africa
- The pharmacokinetics and viral activity of tenofovir in the male genital tract

5. EPIDEMIOLOGY

- Epidemiology of human papillomavirus infection among fishermen along Lake Victoria Shore in the Kisumu District, Kenya

6. POLITICS AND POLICY

- NIH in the dark over conflicts of interest
- FDA considering establishing Indian presence

7. HIV/AIDS FUNDING

- AIDS experts wonder if some of their billions should be shifted to basic health problems

8. PHARMACEUTICAL INDUSTRY

- FDA approves HIV drug etravirine

9. ANNOUNCEMENTS

- amfAR Announces Inaugural Mathilde Krim Fellowship Awards for AIDS Research
- Dr. Rajeev Venkayya Joins Gates Foundation as Director of Global Health Delivery
- Interns needed to support HIV care and research in Zambia: Now accepting applications for HIVCorps 2008-2009
- January Issue of Peer Review Notes from NIH/CSR is Now Online

1. ALLIANCE UPDATES AND COMMUNITY NEWS

Industrialization Symposium at Microbicides 2008

http://www.microbicide.org/meetings/industrializing_microbicides.shtml

The Alliance for **Microbicide** Development invites you to attend Industrializing **Microbicides**, a pre-conference symposium organized by the Alliance to be held at the **Microbicides** 2008 Conference in New Delhi, India on 24 February 2008 from 9:00 to 15:00.

The objectives of the symposium are:

1. To provide an overview of the industrialization process, its components, and how each affects **microbicide** approval, commercialization, and access; and
2. To offer a platform to discuss commercialization challenges and opportunities with **microbicide** developers and

potential manufacturers.

General Information/Registration: To register, view the program, or learn more about this symposium, please visit: http://www.microbicide.org/meetings/industrializing_microbicides.shtml (the PDF with symposium information is available at <http://www.microbicide.org/microbicideinfo/reference/IndustrializingSaveDateDec17final.pdf>).

Registration is required to attend the symposium. Registration will begin on 29 January and can be completed (1) online, (2) by mail/fax, or (3) on-site (if seating is available). Advanced registration is strongly encouraged. For more information, please contact Latifa Boyce, lboyce@microbicide.org, at the Alliance.

The complete Scientific Program for **Microbicides** 2008 is available at http://www.microbicides2008.com/scientific_program.pdf

Population Council's Anticipated Carraguard Timeline

<http://www.popcouncil.org/microbicides/resources.html>

January 2008: The Population Council plans to submit the final clinical study report to the South African Medicines Control Council and the US Food and Drug Administration by the end of January 2008. This must happen before the results are broadly announced.

January or February 2008: After the submission of the regulatory reports, the following groups will confidentially be informed of the key findings prior to the public release of the data:

- * South African government officials (national, provincial, and local health departments and ethics committees)
- * Trial participants and communities
- * Key contacts in allied **microbicides** research and advocacy organizations
- * Selected top-tier journalists in South Africa who cover HIV-related issues.

February 2008: A general announcement will likely come in mid-February 2008, prior to the **Microbicides** 2008 conference and, if possible, may be linked with publication of the results in a scientific journal. A news release will be posted on the Population Council and advocates' web sites, and members of the media will be informed. Results to be presented at **Microbicides** 2008 in Delhi, India at the end of February.

Materials available:

The Population Council has materials that help advocates understand the trial and the organization's **microbicides** program. <http://www.popcouncil.org/microbicides/resources.html> These materials will be updated as the results become available.

The Population Council welcomes your feedback on this plan and any suggestions on how they can work with advocates better. They are also happy to review any materials you may want to develop for your constituents. Please send your questions and any concerns to:

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Barbara Friedland, Phase 3 Behavioral Coordinator, Population Council, New York, bfriedland@popcouncil.org, +1-212-330-0629

Sumen Govender, Clinical Trial Manager, Population Trial, South Africa govenders2@ukzn.ac.za +82 734 8433

[Return to Table of Contents](#)

2. MEDIA COVERAGE OF MICROBICIDES

"Virology: the battle within"

Date: 23 January 2008

Source: *Nature*. 451:388-89.

Author(s): Melinda Wenner

<http://www.nature.com/news/2008/080123/full/451388a.html#B6>

Viral and microbial interactions within living tissues are more complex than previously thought. Melinda Wenner explores whether a periodic table of the infectious could help sort out the mess.

In 2001, Paulo Lusso asked his colleague Leonid Margolis for a favour. Lusso, a virologist at the San Raffaele Scientific Institute in Milan, Italy, had recently discovered that HIV patients are often co-infected with human herpesvirus 6 (HHV-6). Although typically benign, HHV-6 seemed to hasten HIV progression, and no one knew why. Lusso was studying HHV-6's effects on lymphoid cells but wanted to see what the virus did to whole pieces of lymphoid tissue. So he asked Margolis, a virologist at the US National Institute of Child Health and Human Development in Bethesda, Maryland, and an expert on three-dimensional-tissue, to perform some experiments for him.

Margolis agreed. Human lymph-node tissue was hard to come by, but tonsils, which doctors remove from patients all the time, are also lymphoid tissue - and Margolis had developed an experimental tonsil-tissue system to study HIV pathogenesis. Because HHV-6 infection was often found alongside HIV, Margolis and his colleague Jean-Charles Grivel co-infected tonsil tissue with both viruses. He predicted that the herpesvirus, normally suppressed by the immune system, would be free to replicate in immune-compromised HIV-infected tissue.

But, weeks later, when Grivel analysed the infected tissue, something was wrong. HIV wasn't replicating. Although excited, the scientists didn't want to jump to conclusions, so Grivel performed the experiments again. "There was another three weeks of waiting, which was really very emotional," Margolis says. Nevertheless, they got the same result. "We couldn't believe our eyes," Margolis says. HHV-6, at least in this situation, seemed to protect against HIV1.

So infectious agents interact with each other and with hosts in unpredictable ways. An average human body is rife with viruses, and benign and not-so-benign bacteria as well as 'endogenous retroviruses', which buried themselves in the human genome eons ago. This crowded house is a different beast from the sterile cell lines used as models. Scientists such as Margolis therefore argue for a broader approach to virology - one that involves studying infections in a more true-to-life context, predicting their interactions and sometimes taking the unexpected good with the usual bad that infections bring.

That microbes can benefit their hosts is by no means new. For example, bacteria living in the human gut are known to influence immune function, and help our body absorb nutrients. But only recently have scientists suggested that infectious viruses could provide their hosts with benefits as well. Viruses influence the host immune system in significant - and occasionally beneficial - ways, a concept that isn't surprising when one considers that they have been interacting with immune systems for millions of years.

Recently, Herbert 'Skip' Virgin, an immunologist at Washington University School of Medicine in St Louis, Missouri, infected mice with dormant viruses genetically similar to human Epstein-Barr virus and human cytomegalovirus. These viruses, he found, protected the mice from the bacterial pathogens *Listeria monocytogenes* and *Yersinia pestis*. Virgin and his colleagues suggest that the viruses upregulate the production of immune factors that prevent further infection rather than interacting directly with the microbes².

Helping or hindering?

The endogenous retroviruses that cemented their place in human history by infecting the eggs and sperm of our ancestors account for more than 8% of our genome, and some report that as much as half of our genome is composed of fragmented viruses. These viruses seem to influence immune function; for example, the susceptibility of mice to Friend virus, a strain of murine leukaemia virus, is controlled by two genes derived from endogenous retroviruses³. Some have proposed that endogenous retroviruses, long fixed in mammalian genomes, provide the immunosuppression that allows a fetus to develop in its mother's body, despite the differences between the immune systems.

Viruses also interact with each other directly, as Margolis discovered for himself in 2001. Similar viruses sometimes compete with each other, causing one to eventually 'win over' a cell and literally block infection by others. Viruses that are different enough from each other can co-infect cells cooperatively; in a process known as complementation, one virus provides another with a useful protein that it co-opts for its own use. Occasionally, viruses become dependent on other viruses. One such example is hepatitis D, which requires the presence of hepatitis B in order to replicate.

Margolis uncovered why HHV-6 prevents HIV replication under certain conditions. A subtype of HIV, most often found in early infection, generally gains entry into the cell by binding the receptor CCR5. When HHV-6 infects first, however, it instigates production of an immune chemical that binds to CCR5 receptors, blocking HIV's access. HIV can develop resistance to this chemical over time and HHV-6 co-infection may exert selective pressure on HIV to become immune-resistant, or switch to a different co-receptor - a change accompanied by increased HIV virulence. This explains the often poor prognosis of patients infected by both viruses.

Other human viruses influence HIV replication. Margolis found that human herpesvirus 7 (HHV-7) inhibits HIV replication, albeit via a different mechanism from HHV-6 (ref. 4). In 1998, two groups independently reported that HIV patients infected with a seemingly innocuous hepatitis-like virus called GBV-C live longer, although neither group knew why. The studies piqued the interest of Jack Stapleton, director of the University of Iowa's Helen C. Levitt Center for Viral Pathogenesis and Disease in Iowa City, who was, at the time, running an AIDS clinic while studying hepatitis C-HIV interaction.

"We thought it was a statistical fluke and that it wouldn't hold up in a larger study," Stapleton recalls. With access to hundreds of samples, Stapleton decided to replicate the GBV-C study on a group of 362 HIV patients from his clinic. What he found surprised him and confirmed the findings: "If patients had [GBV-C], they were three times more likely to be alive at follow-up," he says⁵. Stapleton's subsequent research, along with work completed by a group in Germany, has shown that a GBV-C peptide interferes with early replication of HIV, and that GBV-C, like HHV-6, increases production of an immune chemical that blocks HIV's entry into the cell.

Always dangerous

No one would suggest purposefully infecting individuals with a persistent infection to ward off HIV. After all, one of the hallmarks of viruses is that they evolve quickly. "Any virus that is not causing disease has the potential to cause disease," says Robert Gallo, director of the Institute of Human Virology at the University of Maryland School of Medicine in Baltimore, and the co-discoverer of HIV. That said, Gallo, who worked with Lusso on the HHV-6 discovery, and his team recently tested the immune chemical produced during HHV-6 infection as a vaginal **microbicide** in macaque monkeys and found that it significantly lowered risk of contracting a monkey-infecting version of HIV⁶.

To make further progress, scientists need to expand which viruses they study, and how they study them, Margolis says. They need to use tissue systems that preserve immune function and cellular communication, because cells within tissues communicate with one another differently and have a different architecture than do cells that are cultured in vitro.

Moreover, Margolis suggests, scientists should study infections in tissues harbouring the same persistent viruses present in humans. "If you study a pathogen such as HIV in a cell-culture model where there is no immune system, there is no effect from other microbes that are in the normal state in an infected human," says Stapleton. "You're really missing important factors that will influence the pathogenesis."

What would be ideal, says Margolis, is a table, not unlike Mendeleev's table of the elements, for infectious agents. "I fantasize about creating a periodic table of microbes," he says. Each cell in the table might feature the name of the microbe, the immune factors it affects, the receptors it uses and the signalling systems it incorporates, he says. Just as the elemental version predicts how two substances react with one another, the periodic table of microbes would predict how two microbes interact in the human body.

"It's off the wall, but it could generate enormous insights," says Michael Lederman, the director of the Center for AIDS Research at Case Western Reserve University in Cleveland, Ohio. Other scientists say that although such a table may have some practical value, the concept is potentially more interesting as a catalyst for scientific ideas and approaches. Philip Murphy, chief of the Laboratory of Molecular Immunology at the US National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, says that scientists can only get so far with existing tissue and animal models. "Pathogens are very host-limited, so there is a whole range of human pathogens that you could never do an experiment with in mice models," he says. For example, although Margolis's lymphoid-tissue model is incredibly useful, he says, there are a number of pathogens that will never infect lymphoid tissue. Scientists will, in other words, need to get creative.

Expanding the study of virology in these ways is challenging for other reasons, too. It is difficult, for example, for a scientist with expertise in DNA viruses such as herpesviruses to study their interactions with RNA viruses such as HIV. But collaboration can help, and although broadening the context of virology might make experiments more complicated, it will also make them more realistic, Margolis says. "In a more complicated system, you probably can understand less," he admits. "But what you understand is really relevant."

EDITOR'S NOTE: References for this article are available at the above website.

"Time for microbicide development"

Date: 18 January 2008

Source: *Housing Works AIDS Issues Update*

<http://www.thebody.com/content/art44826.html?mtrk=5334069>

The **Microbicide** Development Act, in one form or another, has been introduced during eight different Congressional sessions. But now that the legislation has an unprecedented 74 cosponsors in the House and 18 in the Senate, advocates say the time is ripe to get it passed. More than 150 organizations, including Housing Works, Alliance for **Microbicide** Development, and the South Suburban HIV/AIDS Regional Coalition signed on to a letter to Energy and Commerce Committee Chairman Joe Barton, urging him to mark up and report out of committee the **Microbicide** Development Act, H.R. 1420. Illinois Rep. Jan Schakowsky (D-IL) introduced the most recent House version, and Sen. Barack Obama (D-IL) introduced the Senate version. (And for all you bird doggers out there, though Sen. Hillary Clinton (D-NY) is a cosponsor, Sen. John McCain (R-AZ) is not).

Microbicides are products that can prevent transmission of HIV and other infections when used in the vagina or rectum. They include gels, creams, and rings that release drugs slowly over days or weeks, and could give people -- particularly women -- control over HIV prevention, especially in situations where it is difficult or impossible to demand condom use from their partners.

In the 2008 fiscal year budget about \$140 million was earmarked for **microbicide** research and development. The MDA asks for a coordinated unit devoted to **microbicides** within the National Institute of Health's National Institute of Allergies and Infectious Diseases. Currently, research and development is scattered throughout the U.S. Agency for International Development, the Centers for Disease Control and Prevention and the NIH, leaving open the possibility of duplication of work and resources.

"Such coordination, coupled with steady funding for **microbicide** development and the required clinical trials, is essential to ensure the efficient use of tax dollars to develop safe and effective **microbicides**," the letter reads.

Advocates hope that the MDA's passage would spur additional research and excitement around **microbicides**. "It would set precedent, and shows a commitment to doing **microbicide** research and development," said Jessica Terlikowski, policy manager at the AIDS Foundation of Chicago, who is involved with gathering support for the MDA.

"If the MDA passes, it will help to ensure that the U.S. government's commitment to **microbicide** research and development is substantially increased," said Adeyemi Oshodi the Policy and Advocacy Associate at PATH, an international nonprofit, which houses the Global Campaign for **Microbicides**.

Microbicides Desperately Needed

In recent years, there has been momentum behind developing **microbicides** -- with Bill Gates' a particularly effective cheerleader, speaking at length about the promise of vaginal **microbicides** at the 2006 International AIDS Conference -- but an effective **microbicide** has yet to be developed. There are currently two vaginal **microbicides** in phase three trials -- Carraguard gel, sponsored by the Bill and Melinda Gates Foundation, NIAID and the Population Council and Pro2000/5 gels, sponsored by Indevus Pharmaceuticals, the U.K Medical Research Council and Department for International Development. For a chart of all of the **microbicides** in the pipeline click [here](#).

And though most of the emphasis has been on vaginal **microbicides** -- in fact the text of the MDA doesn't mention a word about men -- advocates stress the importance of including rectal **microbicides** for both men and women who have anal sex. This is particularly essential in the U.S. and other countries where men who have sex with men account for the majority of all new infections.

"It's highly unlikely a vaginal product could be used for anal sex," Terlikowski said. "It's important to make sure the funding is there for both."

[Return to Table of Contents](#)

3. PUBLISHED RESEARCH: MICROBICIDE-SPECIFIC

"Acceptability of microbicides among Zambian women"

Author(s): Jones DL, Weiss SM, Chitalu N, et al

Reference: N/A 35(2):147-53.

<http://www.stdjournal.com/pt/re/std/abstract.00007435-200802000-00008.htm;jsessionid=HYXJIJRSVXzBQ8NsFyq4v0cWHxPJPgJPLH5xSnzzMqj4hnpvy8Tk!101667287!181195629!8091!-1>

Published Abstract: *Objectives and Goal:* This study assessed the acceptability after the use of vaginal lubricants as surrogates for **microbicides** among women in Zambia and the role of cultural factors as facilitators or impediments to their potential use for HIV risk reduction within the Zambian context. *Study Design:* HIV seronegative women (N = 301) recruited from the University Teaching Hospital HIV Voluntary Counseling and Testing Center were randomized into group, individual, or enhanced usual care arms. Participants attended pre- and post-HIV test counseling, followed by a 3-session, 2-hour once-a-month intervention introducing them to vaginal lubricants (2 types of gels, suppositories) in addition to male and female condoms. Supplies were offered at months 4 and 5; assessments were at baseline, 6, and 12 months. *Results:* At baseline, the majority of women reported minimal previous exposure to vaginal products and low levels of condom use. Participants' use of products was influenced by product characteristics and perceived partner acceptability; the majority of participants preferred drier products and suppository delivery systems. The basis for decisions regarding vaginal product acceptability changed over time and followed product exposure, and was greatly influenced by perceptions of partner acceptability. *Conclusion:* Results illustrate the influence of male partners on Zambian seronegative women's preferences for **microbicides** products, and the change in preferred characteristics over time.

"Preclinical evaluation of lime juice as a topical microbicide candidate"

Author(s): Fletcher PS, Harman SJ, Boothe AR, et al

Reference: N/A 5(1):3.

<http://highwire.stanford.edu/cgi/medline/pmid;18190686>

Published Abstract: BACKGROUND: The continued growth of the global HIV epidemic highlights the urgent need to develop novel prevention strategies to reduce HIV transmission. The development of topical **microbicides** is likely

to take a number of years before such a product would be widely available. This has resulted in a call for the rapid introduction of simpler vaginal intervention strategies in the interim period. One suggested practice would be vaginal douching with natural products including lime or lemon juice. Here we present a comprehensive preclinical evaluation of lime juice (LiJ) as a potential intervention strategy against HIV. RESULTS: Pre-treatment of HIV with LiJ demonstrated direct virucidal activity, with 10% juice inactivating the virus within 5 minutes. However, this activity was significantly reduced in the presence of seminal plasma, where inactivation required maintaining a 1:1 mixture of neat LiJ and seminal plasma for more than 5 minutes. Additionally, LiJ demonstrated both time and dose-dependent toxicity towards cervicovaginal epithelium, where exposure to 50% juice caused 75-90% toxicity within 5 minutes increasing to 95% by 30 minutes. Cervicovaginal epithelial cell monolayers were more susceptible to the effects of LiJ with 8.8% juice causing 50% toxicity after 5 minutes. Reconstructed stratified cervicovaginal epithelium appeared more resilient to LiJ toxicity with 30 minutes exposure to 50% LiJ having little effect on viability. However viability was reduced by 75% and 90% following 60 and 120 minutes exposure. Furthermore, repeat application (several times daily) of 25% LiJ caused 80-90% reduction in viability. CONCLUSIONS: These data demonstrate that the virucidal activity of LiJ is severely compromised in the presence of seminal plasma. Potentially, to be effective against HIV in vivo, women would need to apply a volume of neat LiJ equal to that of an ejaculate, and maintain this ratio vaginally for 5-30 minutes after ejaculation. Data presented here suggest that this would have significant adverse effects on the genital mucosa. These data raise serious questions about the plausibility and safety of such a prevention approach.

"Sexual coercion and sexual desire: ambivalent meanings of heterosexual anal sex in Soweto, South Africa"

Author(s): Stadler JJ, Delany S, Mntambo M

Reference: N/A 19(10):1189-93.

<http://www.informaworld.com/smpp/content~content=a788283309~db=all~jumptype=rss>

Published Abstract: Anal sex within heterosexual relationships is usually underreported or not reported at all, yet is increasingly recognised as a potential mode of HIV transmission. Understanding the circumstances of anal sex is critical for trials that seek to assess the efficacy of **microbicides**. This article draws on qualitative data collected during a feasibility study for a clinical trial of **microbicides** in Soweto, South Africa. Focus groups of women enrolled in the feasibility study discussed the circumstances under which they and other women in the community had anal sex. Their narratives drew attention to the ambivalent meanings of anal sex; often regarded as a form of sexual coercion but also frequently as sexual pleasure. The article explores the reasons for these apparent contradictions.

[Return to Table of Contents](#)

4. PUBLISHED RESEARCH: RELEVANT BASIC AND TRANSLATIONAL SCIENCE

"Herpes simplex virus type 2 acquisition during recent HIV infection does not influence plasma HIV levels"

Author(s): Cachay ER, Frost SD, Poon AF, et al

Reference: N/A Epub ahead of print.

http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=Retrieve&db=PubMed&list_uids=18197122&dopt=AbstractPlus

Published Abstract: We assessed the effect of herpes simplex virus type 2 (HSV-2) acquisition on the plasma HIV RNA and CD4 cell levels among individuals with primary HIV infection using a retrospective cohort analysis. We studied 119 adult, antiretroviral-naive, recently HIV-infected men with a negative HSV-2-specific enzyme immunoassay (EIA) result at enrollment. HSV-2 acquisition was determined by seroconversion on HSV-2 EIA, confirmed by Western blot analysis. Ten men acquired HSV-2 infection a median of 1.3 years after HIV infection (HSV-2 incidence rate of 7.4 per 100 person-years of follow-up). The median time of follow-up after acquiring HSV-2 infection was 303 days. All men except 1 were asymptomatic during HSV-2 acquisition, and only 1 HSV-2 seroconverter, who was asymptomatic, had a transient increase in blood HIV load (0.5 log₁₀ copies/mL over 11 days). The HSV-2 incidence rate was high in our cohort of recently HIV-infected individuals; however, HSV-2 acquisition did not significantly change the plasma HIV dynamics and CD4 cell levels.

"Inhibition of HIV-1 infectivity through an innate mechanism involving naturally occurring IgM anti-leukocyte autoantibodies"

Author(s): Lobo PI, Schlegel KH, Yuan W, et al

Reference: N/A 180(3):1769-79.

<http://www.jimmunol.org/cgi/content/abstract/180/3/1769?etoc>

Published Abstract: In prior studies, we show that naturally occurring IgM anti-leukocyte autoantibodies (IgM-ALA) bind to CD3, CD4, CCR5, and CXCR4 receptors. These observations prompted us to determine whether IgM-ALA have a role in inhibiting HIV-1 infectivity by inhibiting viral entry into cells. We show that purified IgM, but not IgG, from individual sera of both normal and HIV-1 infected individuals is highly inhibitory (greater than 95%) to HIV-1 viral infectivity both in vitro using PHA plus IL-2 activated PBL and in vivo using the human PBL-SCID mouse. Inhibition was observed with physiological doses of purified serum IgM and even after IgM was added 3 days postinfection in the in vitro assays. Absorbing purified serum IgM either with leukocytes or immobilized recombinant CD4 significantly decreased (greater than 80%) the inhibitory effect on HIV-1 infectivity. IgM inhibited by greater than 90% syncytia formation with the X4-IIIB infected SupT-1 cells indicating therefore that IgM inhibits viral attachment to core-receptors. IgM mediated anti-HIV-1 activity was highly specific as only certain IgM-ALA, obtained from human B cell clones inhibited HIV-1. IgM from certain HIV-1 infected individuals were not inhibitory to some R5-HIV-1 viral strains indicating that certain HIV-IgM may lack Abs reactive to strain specific coreceptor epitopes. These data indicate that an innate immune mechanism which is present from birth i.e., IgM-ALA, has a role in inhibiting HIV-1 viral entry into cells. Validation of this data with other in vivo models will be needed to determine whether in vivo administration or enhancement of IgM-ALA, e.g., through a vaccine, could prolong the asymptomatic state in HIV-1 infected individuals.

"The association between school attendance, HIV infection and sexual behaviour among young people in rural South Africa"

Author(s): Hargreaves JR, Morison LA, Kim JC, et al

Reference: N/A 62(2):113-19.

<http://jech.bmj.com/cgi/content/abstract/62/2/113?rss=1>

Published Abstract: Objectives: To investigate whether the prevalence of HIV infection among young people, and sexual behaviours associated with increased HIV risk, are differentially distributed between students and those not attending school or college. Design: A random population sample of unmarried young people (916 males, 1003 females) aged 14-25 years from rural South Africa in 2001. Methods: Data on school attendance and HIV risk characteristics came from structured face-to-face interviews. HIV serostatus was assessed by oral fluid ELISA. Logistic regression models specified HIV serostatus and high-risk behaviours as outcome variables. The primary exposure was school attendance. Models were adjusted for potential confounders. Results: HIV knowledge, communication about sex and HIV testing were similarly distributed among students and non-students. The lifetime number of partners was lower for students of both sexes (adjusted odds ratio (aOR) for more than three partners for men 0.67; 95% CI 0.44 to 1.00; aOR for more than two partners for women 0.69; 95% CI 0.46 to 1.04). Among young women, fewer students reported having partners more than three years older than themselves (aOR 0.58; 95% CI 0.37 to 0.92), having sex more than five times with a partner (aOR 0.57; 95% CI 0.37 to 0.87) and unprotected intercourse during the past year (aOR 0.60; 95% CI 0.40 to 0.91). Male students were less likely to be HIV positive than non-students (aOR 0.21; 95% CI 0.06 to 0.71). Conclusions: Attending school was associated with lower-risk sexual behaviours and, among young men, lower HIV prevalence. Secondary school attendance may influence the structure of sexual networks and reduce HIV risk. Maximising school attendance may reduce HIV transmission among young people.

"The pharmacokinetics and viral activity of tenofovir in the male genital tract"

Author(s): Vourvahis M, Tappouni HL, Patterson KB, et al

Reference: N/A Epub ahead of print.

http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=Retrieve&db=PubMed&list_uids=18197124&dopt=AbstractPlus

Published Abstract: OBJECTIVE:: To measure tenofovir (TFV) concentrations in the male genital tract (GT) after single and multiple doses of tenofovir disoproxil fumarate (TDF) and evaluate the HIV-1 RNA response to monotherapy. DESIGN AND METHODS:: A pharmacokinetic study of blood plasma (BP) and GT TFV concentrations in 9 men was conducted after 1 and less than or equal to 14 doses of TDF. TFV concentrations were measured by validated high-performance liquid chromatography-ultraviolet or tandem mass spectrometry methods, and HIV-1 RNA was measured using Roche (Roche Molecular Systems, Branchburg, NJ) or bioMerieux (bioMerieux, Durham, NC)

kits. RESULTS:: TFV GT concentrations were 4.4-fold +/- 5.1-fold higher than BP after dose 1 and 5.1-fold +/- 6.8-fold higher than BP after dose 14. Intracellular GT TFV-diphosphate concentrations were 9.4-fold higher than BP after dose 1 and 17.5-fold +/- 22.6-fold higher after dose 7. After 14 days of TDF monotherapy, HIV-1 RNA decreased by 0.9 log₁₀ copies/mL in blood and 1.0 log₁₀ copies/mL in the GT. CONCLUSIONS:: High TFV concentrations were achieved rapidly in the GT of all subjects after single and multiple doses and potently reduced BP and GT HIV-1 RNA levels.

[Return to Table of Contents](#)

5. EPIDEMIOLOGY

"Epidemiology of human papillomavirus infection among fishermen along Lake Victoria Shore in the Kisumu District, Kenya"

Author(s): Ng'ayo MO, Bukusi E, Rowhani-Rahbar A, et al

Reference: N/A 84(1):62-6. Epub ahead of print.

<http://sti.bmj.com/cgi/content/abstract/84/1/62?ct=ct>

Published Abstract: *Objectives:* The epidemiology of human papillomavirus (HPV) infection in men in Kenya is largely uncharacterised. We set out to determine the prevalence and determinants of HPV infection among sexually active fishermen along Lake Victoria in the Kisumu district of Kenya. *Methods:* Genital swabs were obtained from 250 consenting fishermen from 18 beaches and a detailed sociodemographic questionnaire was administered. HPV positivity was determined by polymerase chain reaction amplification and detected by dot blot hybridisation with generic HPV and beta-globin probes. HPV positive samples were genotyped using the Roche Linear array assay. *Results:* Overall, 144 (57.6%) fishermen had detectable HPV DNA, 106 (42.4%) were infected with oncogenic HPV types, with HPV-16 being the most frequent type (12.4%). Among HPV positive men, 105 (72.9%) were infected with more than one HPV type and 20 (13.9%) were infected with more than six different types. HIV seropositive men (PR 1.49, 95% CI 1.19 to 1.86) and those divorced or separated (PR 1.62, 95% CI 1.13 to 2.33) were more likely to be infected with HPV. HIV infection (PR 1.22, 95% CI 1.01 to 1.47) was the only factor independently associated with infection with multiple types of HPV. *Conclusion:* The prevalence of oncogenic HPV infection is high among this population and is associated with HIV serostatus and marital status. This community could benefit from enhanced sexually transmitted infection and HIV prevention interventions.

[Return to Table of Contents](#)

6. POLITICS AND POLICY

"NIH in the dark over conflicts of interest"

Date: 23 January 2008

Source: *Nature*. 451:306.

<http://www.nature.com/news/2008/080123/full/451386a.html>

The US National Institutes of Health (NIH) relies on an honour system that leaves it unaware of the details of situations in which its external grantees have financial conflicts of interest, according to a report released on 17 January.

The report, from the inspector-general of the Department of Health and Human Services, found that nearly half of the NIH's 24 grant-making institutes and centres were unable to provide any of the financial disclosure reports they received from external institutions between 2004 and 2006. Of the 438 reports that were produced, 89% were devoid of details describing the conflicts or how they were being managed.

Such details are not required under current rules; the report recommended that this change. But the NIH disputed that advice, saying that if it agreed to accept detailed reports, it would be held accountable for oversight duties that are properly the job of grantees' institutions.

"FDA considering establishing Indian presence"

Date: 21 January 2008

Source: *in-Pharma Technologist.com*

Author(s): Kirsty Barnes

<http://in-pharmatechnologist.com/news/ng.asp?id=82658>

The US Food and Drug Administration (FDA) is considering establishing a presence in India, amidst the country's growing ties with the US pharma industry. FDA commissioner Andrew Von Eschenbach and US Health and Human Service (HHS) secretary Michael Leavitt have been visiting India to assess the manufacturing practices at some of the facilities there.

The visit was largely initiated in response to mounting apprehension over the quality of both food and drugs and related ingredients being imported into the US. The current import protection system was described by Leavitt as "inadequate." Some Indian media reports have also claimed that the visit was made because the FDA is planning on setting up an office in the country. On the flip side, other media reports have said that the FDA is not planning such a move.

Outsourcing-Pharma.com confirmed with an FDA spokesperson that at this point the agency is just offering advice and guidance to the Indian authorities who are looking at setting up a regulatory body that is comparable to that of the FDA.

During his trip to India last week, Leavitt stated: "Basically, we would be glad to try to provide technical assistance to the Indian government as it further develops its new regulatory agency/ies." He also said that "we are considering trying to establish an FDA presence/office in India," although no decision has been made as yet, the spokesperson advised.

Mr Eschenbach also said that any move made by the FDA in this regard would be aimed at "building a bridge, not a barrier to bring the fruits of science and technology to people". The FDA has been active of late in attempting to play catch up on keeping a watchful eye over the globalisation of drug manufacturing which has rocketed in the past 20 years.

75-80 per cent of all active pharmaceutical ingredients (APIs) used by US drug manufacturers are now imported, mainly from India and China, along with 40 per cent of finished dosage forms from various global locations. At present, however, the FDA does not regularly inspect all foreign facilities manufacturing the APIs serving them (generally only at intervals of five years or longer) and many foreign facilities have never been inspected at all, claim the Synthetic Organic Chemical Manufacturers Association (SOCMA) and the European Fine Chemicals Group (EFCG), who are demanding that regulators increase their inspections of such foreign facilities.

Furthermore, 90 per cent of the inspections carried out by the FDA are pre-approval inspections, while only 10 per cent are for cGMP compliance purposes, according to Joe Acker, President of SOCMA. Moreover, A US government audit recently confirmed the FDA's continual lack of inspection of foreign drug manufacturing plants. In the Government Accountability Office (GAO) audit report, it was revealed that at present the FDA only carries out inspections of around 7 per cent of the total number of foreign drug manufacturers a year.

China, which has the largest number of drug manufacturers eligible for FDA inspection (714) was earmarked for only 13 regulatory visits by the FDA in 2007, meaning only less than 2 per cent of the country's drug exporters will have had their facilities examined. The FDA has been working with its Chinese counterpart, the State Food and Drug Administration (SFDA), to address the issue, the first steps in tightening the safety controls on the pharmaceutical ingredients imported to the US from China being taken in December following months of negotiations between the regulatory bodies of the two countries.

From now on, Chinese manufacturers that export to the US any of the APIs listed on a newly drawn up list are required to register with the Chinese drug regulators. Gentamicin sulphate (an antibiotic), atorvastatin (the API in Lipitor) and sildenafil (the API in Viagra), are among the big-name ingredients included on the list. The agreement is only a small step in the direction of a number of measures that need to be taken to secure the supply chain, but it will at least assist the regulatory agencies of both countries in more easily keeping track of and inspecting a larger number of manufacturers as to their regulatory compliance and hence ensure safer medicines.

The FDA has already recently opened an office in China, which should also improve the situation, so an Indian office would be a likely next move.

[Return to Table of Contents](#)

7. HIV/AIDS FUNDING

"AIDS experts wonder if some of their billions should be shifted to basic health problems"

Date: 18 January 2008

Source: *Associated Press*

<http://www.ihf.com/articles/ap/2008/01/18/europe/EU-MED-Rethinking-AIDS.php>

In the two decades since AIDS began sweeping the globe, it has often been labeled as the biggest threat to international health. But with revised numbers downsizing the pandemic published last year - along with an admission that AIDS peaked in the late 1990s - some AIDS experts are now wondering if it might be wise to shift some of the billions of dollars of AIDS money to basic health problems like clean water, family planning or diarrhea.

"If we look at the data objectively, we are spending too much on AIDS," said Dr. Malcolm Potts, an AIDS expert at the University of California in Berkeley, who once worked with prostitutes on the front lines of the epidemic in Ghana. Problems like malnutrition, pneumonia and malaria kill more children in Africa than AIDS. "We are programmed to react quickly to small children with AIDS in distress," Potts said. "Unfortunately, we don't have that same reaction when looking at statistics that tell us what we should be spending on."

The world invests about US\$8 billion to US\$10 billion into AIDS every year, more than 100 times what it spends on clean water projects in developing countries. Yet more than 2 billion people do not have access to adequate sanitation, and about 1 billion lack clean water.

In a recent series in *The Lancet*, experts wrote that more than one-third of child deaths and 11 percent of the total disease burden worldwide are due to mothers and children not getting enough to eat - or not getting enough nutritional food.

"We have a system in public health where the loudest voice gets the most money," said Dr. Richard Horton, editor of *The Lancet*. "AIDS has grossly distorted our limited budget."

But some AIDS experts argue that cutting back on fighting HIV would be dangerous.

"We cannot let the pendulum swing back to a time when we didn't spend a lot on AIDS," said Dr. Kevin De Cock, director of the AIDS department at the World Health Organization. "We now have millions of people on treatment and we can't just stop that." Still, De Cock once worked on AIDS projects in Kenya, his office just above a large slum. "It did feel a bit peculiar to be investing so much money into anti-retrovirals while the people there were dealing with huge problems like water and sanitation," De Cock said.

Part of the issue is advocacy. From celebrity ambassadors to red ribbons, other diseases have been left by the wayside.

"No one is beating the drum for basic health problems," said Daniel Halperin, an AIDS expert at the Harvard University's School of Public Health.

Aside from southern Africa, most of the continent has relatively low rates of HIV, and much higher rates of easily treatable diseases like diarrhea and respiratory illnesses. Yet much of the money from the West, especially from the

United States, goes into AIDS. President George W. Bush has requested another US\$30 billion for the next five years for AIDS, mostly to be spent in Africa, and the leading Democratic candidates have proposed that figure be bumped up to US\$50 billion. In comparison, the President's Malaria Initiative, launched in 2005, aims to reduce malaria deaths by half in 15 African countries. Its five-year budget is an estimated US\$1.2 billion.

Halperin recently wrote a commentary on the imbalance in AIDS spending versus other public health problems, published in the New York Times, and said he was astounded by the response. Most of the responses were positive, he said, with many AIDS experts agreeing it was time to re-examine spending. Most AIDS officials say the solution is to boost the budget for all of public health.

"Why does the public health budget have to be so limited?" asked Tom Coates, a professor of global AIDS research at the University of California in Los Angeles. "Let's not drag AIDS care and prevention down to the level of every other disease, but let's bring everything else up to the level of AIDS." That may be wishful thinking.

"At the end of the day, there are limits to how big the public health pie can be," Halperin said. "And meanwhile, there are important trade-offs to consider."

African doctors say that AIDS money has created parallel health systems, where AIDS patients may get free drugs, but people with other diseases are often forced to pay out of pocket. Since the discovery of anti-retrovirals to fight HIV in the 1990s, AIDS has virtually become a chronic, treatable disease in the West. But the disease has not been conquered so easily in Africa. Not only are the anti-AIDS drugs too expensive for most patients, but major problems in the health system need to be fixed first.

"It's hard to get Western donors to listen," said Dr. Richard Wamai, a Kenyan doctor at Harvard University's School of Public Health. Wamai said that some African health infrastructures are so weak they cannot absorb the donations, meaning that AIDS drugs are sometimes left sitting in warehouses because governments cannot distribute them. Still, "trying to redirect AIDS money will take a long time," Wamai said. "It's a bit like trying to stop an ocean liner."

[Return to Table of Contents](#)

8. PHARMACEUTICAL INDUSTRY

"FDA approves HIV drug etravirine"

Date: 19 January 2008

Source: *Associated Press*

http://www.boston.com/news/health/articles/2008/01/19/fda_approves_hiv_drug_etravirine/?p1=email_to_a_friend

Tablets of the drug etravirine were approved Friday by the Food and Drug Administration for the treatment of HIV infection in adults who have failed treatment with other antiretrovirals. Sold under the trade name Intelence, etravirine is a non-nucleoside reverse transcriptase inhibitor, or NNRTI, that helps to block an enzyme that the human immunodeficiency virus needs to multiply, the FDA said. It was approved for use in combination with other anti-HIV

medications.

Etravirine can reduce the amount of HIV in the blood and increase white blood cells that help fight off other infections, the FDA said. It also may reduce the risk of death or infections that can occur with a weakened immune system. The government gave etravirine a priority review, a status granted to medications aimed at treating serious or life-threatening conditions. Tibotec Pharmaceuticals Ltd., a unit of Johnson & Johnson, said last July that it had requested etravirine be placed on a fast track for review.

"This is another significant new product for many HIV-infected patients who are NNRTI-resistant and whose infections are not responding to currently available medications," said Dr. Debra B. Birnkrant, director of the FDA's Division of Antiviral Products.

The drug is distributed by Tibotec Therapeutics, a division of Ortho Biotech Products, L.P., a Johnson and Johnson company based in Bridgewater, N.J.

[Return to Table of Contents](#)

9. ANNOUNCEMENTS

amfAR Announces Inaugural Mathilde Krim Fellowship Awards for AIDS Research

<http://www.amfar.org/cgi-bin/iowa/news/press.html?record=186>

New York City, January 4, 2008 - amfAR, the Foundation for AIDS Research, has announced that it will award more than \$1 million in the inaugural round of Mathilde Krim Fellowships in Basic Biomedical Research. Named in honor of amfAR's founding chairman, Dr. Mathilde Krim, the Krim Fellowship program is a new research initiative created to support bright young scientists seeking innovative prevention and treatment solutions to HIV/AIDS. Since the early days of the epidemic, Dr. Krim has been a leading advocate of increased support for research on a disease that others have often preferred to ignore.

"amfAR was overwhelmed by the extraordinarily high caliber of proposals submitted," said Dr. Rowena Johnston, amfAR's vice president of research. "This response underscores the urgent need for support of young researchers who bring fresh ideas and vigor to the field and who represent the future of HIV/AIDS research."

amfAR initiated the new program in response to the dwindling sources of support that are available to young scientists. Yet these same young researchers are often those with the most innovative and daring ideas - ideas that have breakthrough potential. With Mathilde Krim Fellowship support, these future leaders of AIDS research will be searching for new drug treatment candidates, looking to optimize vaccine design, and even investigating barriers to a cure for HIV infection.

"amfAR has a long and proud history of supporting innovative research," said amfAR CEO Kevin Robert Frost. "Our new Krim Fellowship program continues that tradition and takes it to a higher level. It is also a fitting tribute to the vision and unwavering commitment to research of our founding chairman."

Since it was founded in 1985, amfAR has supported the early studies behind almost every significant breakthrough in the treatment of HIV/AIDS, including studies that were critical to the development of protease inhibitors, the powerful drugs that revolutionized the treatment of HIV/AIDS; pioneering research that led to the use of AZT to block mother-to-child transmission of HIV, resulting in the virtual elimination of this form of HIV transmission in the industrialized world; and studies that identified the essential role of the CCR5 co-receptor, on which one of the newest HIV therapies, maraviroc, is based.

EDITOR'S NOTE: The full list of recipients of the 2008 Fellowships are available at the above website.

Dr. Rajeev Venkayya Joins Gates Foundation as Director of Global Health Delivery

<http://www.gatesfoundation.org/GlobalHealth/Announcements/Announce-080122.htm>

The Bill and Melinda Gates Foundation announced today that Dr. Rajeev Venkayya has joined the Global Health Program as director of Global Health Delivery. Dr. Venkayya is a medical doctor and former coordinator of U.S. government medical and public health efforts, including preparations for a potential influenza pandemic.

Dr. Venkayya will oversee the Gates Foundation's efforts to help expand the availability of, and access to, effective vaccines, drugs, and other health solutions in the developing world. He will also lead efforts to prepare for delivery of future health solutions.

"A number of important health interventions currently in late-stage development could be on the market in the next several years. We want to ensure that these life-saving solutions reach those who need them most," said Dr. Tachi Yamada, president of the foundation's Global Health Program. "Rajeev brings a wealth of experience as both a physician and senior health policy strategist, and we're fortunate to have him heading our efforts in this area."

The foundation's Global Health Delivery team coordinates late-stage development of foundation-funded health technologies and interventions through clinical trials and regulatory approval. The Delivery team also identifies ways to ensure adequate financing to purchase vaccines and drugs, strengthen health supply and distribution systems, address shortages of health workers, and increase public awareness about health.

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EDITOR'S NOTE: The full text of this announcement is available at the above website.

Interns needed to support HIV care and research in Zambia: Now accepting applications for HIVCorps 2008-2009

http://www.cidrz.org/cidrz_internship

Established in 1999, the Centre for Infectious Disease Research in Zambia (CIDRZ) is a Zambian organization affiliated with the University of Alabama at Birmingham (UAB). CIDRZ's work includes research, training and service delivery in the areas of HIV/AIDS prevention and treatment and maternal-child health. CIDRZ has experienced phenomenal growth in recent years, garnering over \$115 million in grant funding for our work in Zambia. Our faculty and collaborators are among the world's leading thinkers on issues related to the prevention of HIV transmission from mother to child and HIV/AIDS treatment programs in developing countries.

Now entering its 5th year, the CIDRZ HIVCorps* initiative has trained over 80 expatriate and Zambian interns. The program provides students and recent graduates the opportunity to participate in international HIV programs or research. Individuals with an interest in the following programmatic areas are encouraged to apply: (1) pediatric antiretroviral therapy scale-up, (2) tuberculosis and HIV co-infection, (3) HIV-related community outreach programs, (4) monitoring of clinical care during rapid scale-up, (5) data management and outcomes analysis, (6) perinatal HIV prevention services, (7) HIV/AIDS clinical trials, (8) women's reproductive health, (9) laboratory systems in the developing world, and (10) grant writing and program development.

The HIVCorps internship is targeted at medical, nursing or MPH students who are able to delay their studies for a year, recent graduates of the above programs who wish to gain international experience, and college graduates (including those graduating from post-baccalaureate programs) with substantial skills or experience. Applicants with experience in project management, public health, community outreach, study coordination, data management, statistical analysis, scientific writing, and laboratory work are particularly encouraged to apply. Previous international experience is beneficial but not a requirement. Between 6 and 10 interns will be selected for 2008-2009. Work will be based in Lusaka, Zambia, though travel to various parts of the country may be required.

Duration: 10-12 months (with allowances made for medical / graduate school interviews if needed). All applicants must be available to start in early July 2008. Compensation: Interns receive \$1000 each month for basic living expenses and international airfare to Zambia. Group housing, costs related to program activities, and local and emergency evacuation insurance will be provided.

Application Procedures: Send your completed application form to Maria Lombe, administrative coordinator (maria.lombe@cidrz.org). Deadline for applications is February 28, 2008. Phone interviews will be conducted for selected applicants; final decisions are expected in April 2008. Contact Information: For additional information or questions regarding HIVCorps, contact Maria Lombe. For a more detailed description of CIDRZ activities, please check our website at www.cidrz.org.

January Issue of Peer Review Notes from NIH/CSR is Now Online

<http://cms.csr.nih.gov/NewsandReports/PeerReviewNotes/>

The NIH Center for Scientific Review publishes Peer Review Notes to inform reviewers, NIH staff and others interested in news related to our grant application review policies, procedures and plans. Comments may be sent to Don Lockett, Communications Director, Center for Scientific Review, National Institutes of Health. E-mail: Lockettd@csr.nih.gov

[Return to Table of Contents](#)