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Johnson & Johnson Takes Heat from Doctors Without Borders for Not Sharing HIV Drug Patents

Johnson & Johnson (J&J) holds patents on three “important HIV drugs” that could benefit patients in the developing world, if they were more affordable, says Doctors Without Borders (DWB).

Pricier, newer drugs to treat HIV/AIDS are beyond the reach of most people in the poorest regions of the world, where patients often must take older, more toxic medicines. In addition, developing-world patients who become resistant to their existing drugs often have few options.
New Brunswick, N.J.-based J&J holds key patents on rilpivirine, a first-line HIV drug, as well as darunavir and etravirine, which are used to treat patients who have become resistant to their first-line medicines. In February, a J&J subsidiary agreed to provide three generic drug firms with rights to manufacture and distribute a low-cost version of rilpivirine. The deal should help patients in sub-Saharan Africa, home to about 68 percent of the world’s HIV population.

Judit Rius, US manager of DWB’s Access to Essential Medicines Campaign, said the agreement is too restrictive, covers only part of Africa, and does not go far enough in reducing costs for the people it targets. “We think there is a better way to do it,” she said.

DWB has created a drug patent pool for HIV drugs, including pediatric formulations and versions that combine several medicines in a single pill. The pool works by licensing patents to multiple drugmakers and creating enough competition to bring prices down. Rius said Roche and Gilead have agreed to join DWB’s pool, but J&J, Merck, and Bristol-Myers Squibb have not.

**Vietnam Fails to Prevent Spread of HIV Among Sex Workers**

*Deutsche Presse-Agentur*, (04.28.2011)

The HIV rate among sex workers in Vietnam’s major cities remains stubbornly high, despite efforts to curb infections.

A Labor Ministry report presented at a UN- and government-sponsored conference in Hanoi on April 28 said approximately 0.3 percent of sex workers across Vietnam are HIV-infected. But in Hanoi, Ho Chi Minh, and Hai Phong, the rates jump to 20 percent, 16 percent, and 23 percent, respectively.

Ministry spokesperson Nguyen Trong Dam told the state-run newspaper Viet Nam News that a lack of coordination among various government agencies working on HIV/AIDS prevention is part of the problem. Another factor is that too many people are still not using condoms, he said.

According to the report, condoms are not easily accessible in hotels, and cultural barriers prevent both sex workers and clients from obtaining them.

Duong Van Dat of the UN Population Fund noted that few Vietnamese sex workers have access to HIV/AIDS prevention tools such as free condoms or STD treatment. Neighboring Cambodia has seen a dramatic drop in cases of HIV and other STDs; some 80 percent of sex workers there report condom use, Dat said.

**More HIV Infections Linked To Injection Drug Use In East Africa, Report Finds**

A growing number of HIV infections in East Africa are linked to injection drug use (IDU), according to a new report (.pdf) from the Center for Strategic and International Studies, *VOA News* reports (DeCapua, 4/29).

CSIS sent a team to study the issue in Kenya and Tanzania "to better understand the dimensions of the IDU-driven HIV epidemic in those two countries and to look at how U.S.-supported programs through PEPFAR are helping shape a response," according to a report summary (4/29).

Report co-author Lisa Carty, deputy director at the CSIS Global Health Policy Center, said, "Globally, we know that [injection drug use] is quite a serious problem. And we know that one in every three new infections is attributable to injecting drug use. We know that in Eastern Europe, Central Asia, the former Soviet Union, it continues to be the major driver of the epidemic there. What we're seeing happen on a parallel track is that in many countries, where the new HIV incidence is starting to stabilize and level off, that the proportion of IDU-related infections is continuing to increase," VOA News reports.

Phil Nieberg, senior associate with the Global Health Policy Center and a co-author of the report, said needle sharing and women engaging in sex work to help pay for drugs are helping to spread the virus, VOA News continues. Injection drug users, as well as sex workers and men who have sex with men, often "go underground or hide" to avoid interaction with law enforcement officials, which takes them further from prevention and treatment programs, the news service writes.

Both authors said "treating addiction as a disease instead of a crime" could allow additional drug users to seek help through counseling, needle and syringe exchange programs, or other harm reduction efforts such as methadone substitution therapy, VOA News reports (4/29).

The team concluded that "recent changes in U.S. policy and guidance that have focused on the linkage of HIV transmission with IDU are playing an important role in helping move the HIV prevention and IDU treatment policies and practices of both countries toward a more evidence-based and effective approach," and recommended several additional measures that could be undertaken to improve the impact of programs, according to the report (April 2011).
Stop Girls From Marrying Young
"Girls who marry young are more likely to become mothers before their bodies have matured, which puts them at higher risk for infant and maternal mortality. Medical complications due to pregnancy are the lead in uptake of grant relating to ban on blood donations by gay and bisexual men

Canadian researchers may be biased since a half-million dollar research grant to possibly change the ban on gay and bisexual men donating blood has not been accessed, states a Salon article in CMAJ (Canadian Medical Association Journal) (pre-embargo link only) http://www.cmaj.ca/embargo/cmaji10262.pdf.

"As to why researchers did not proceed in their normal fashion, which is to fiercely compete for any relevant funding opportunity, remains unknown," write Jason Behrmann and Vardit Ravitsky, University of Montreal. "However, a clue may lie in the fact that this grant aims to support clinical research necessary to justify relaxing the current — hotly contested — ban on gay and bisexual men as eligible blood donors."

Current policies do not allow men who have had sex with men from 1977 to the present to donate blood.

"It's time to prove the claim that members of the gay and bisexual community can become eligible blood donors without increasing risks of transfusion-transmitted infections to the public," write the authors. "Using the funding on offer is the first step in this process."

The authors state that new screening methods allow early detection of HIV and hepatitis B and C which can protect the blood supply from infection.

"This case also provides an illuminating example as to why it is necessary for Canadian guidelines regarding ethical conduct for research involving humans to continue to foster fairness and equity in research," they write. "The guidelines emphasize the principle of justice and the obligation of appropriate inclusion of vulnerable and typically excluded groups in research. Ignoring a grant that encourages the inclusion of sexual minorities in clinical research therefore runs contrary to national standards of scientific excellence."

"While this research may be complex and may pose particular methodologic challenges, the research community should face these challenges, and funding agencies should facilitate the uptake of this opportunity by addressing the needs of researchers. Both researchers and funders should demonstrate social responsibility since this research will have important societal implications and will promote justice and fairness in establishing an evidence-based foundation for blood donation policies," conclude the authors.

Early pregnancy is a leading cause of death among girls ages 15 to 19 worldwide," Tamara Kreinin, executive director of women and population at the U.N. Foundation, writes in a Chicago Tribune opinion piece highlighting the dangers child brides face.

"When we help address the needs of a girl, there is an important ripple effect," according to Kreinin. "Programs designed to specifically address child marriage actually affect a broader range of positive outcomes, including health, education and economic empowerment. Also, programs that provide safe spaces for girls have been shown to delay the age participants marry," she writes before highlighting the U.N. Foundation's Girl Up campaign. "There are 60 million child brides in the world today; that means there are 60 million would-be doctors, teachers and prime ministers who won't have the chance to pursue these dreams. And a world where a girl can achieve her dreams is a better world for us all," she writes (4/29).

HIV risk in young black males
Notions about partner's masculinity may affect condom use
DENVER – New research is shedding light on why young black males who have sex with males have among the highest rates of HIV infection in the United States, even though their reported use of condoms is similar to males of other racial and ethnic backgrounds.

A key factor may be black men's cultural beliefs about masculinity, which may influence how they choose their sex partners, make judgments about HIV risk and make decisions about condom use, according to a study to be presented Monday, May 2, at the Pediatric Academic Societies (PAS) annual meeting in Denver.

Young black males who have sex with males have twice the number of new HIV infections as young Hispanic and white men who have male partners, according to Errol L. Fields, MD, PhD, MPH, lead
author of the study and a pediatric resident at Children's Hospital Boston and Boston Medical Center. They also are five times more likely to be HIV-infected than white males of similar ages.

"We interviewed young black men to hear the stories behind these statistics," Dr. Fields said. Thirty-five black males ages 18-24 years in New York City, upstate New York and Atlanta took part in semi-structured interviews that explored cultural and psychosocial factors that may influence how they choose sexual partners, assess HIV risk and decide whether to use condoms.

Most of those interviewed said they preferred to partner with men whom they perceived as masculine. Some of the young men said they allowed partners who were more masculine to control what sexual activity they engaged in and whether they used condoms.

"We found that their beliefs about masculinity may affect their ability to protect themselves against HIV," Dr. Fields said. "For example, many believed that men who acted more feminine were at greater risk for HIV than men who acted more masculine. These beliefs may have led to greater risk behavior with men who were perceived to be masculine because they believed these men were less likely to have HIV."

The study findings suggest that cultural beliefs about masculinity may affect HIV risk in black adolescents and young adult males who have male sexual partners and should be considered in prevention strategies directed toward this population, Dr. Fields concluded.

**Scientists show that HIV drugs can also target tropical parasites**

New research in the FASEB Journal suggests the protein Ddi 1 from Leishmania parasites is sensitive to anti-HIV inhibitors and could be target for malaria and other parasitic diseases

Scientists have discovered that drugs used to treat HIV may also one day become lifesaving drugs targeted at parasitic diseases such as leishmaniasis and malaria. According to new research published in The FASEB Journal (http://www.fasebj.org), scientists have identified the target of action for some anti-HIV drugs with known abilities to kill serious pathogenic parasites. While scientists have long known that these HIV drugs can kill parasites, exactly how they work was previously unknown. Researchers discovered that a particular protein called Ddi 1 from Leishmania parasites is sensitive to anti-HIV inhibitors. This research could one day significantly change the treatment of parasitic diseases.

"People in developing countries can be exposed to parasitic diseases such as malaria and leishmaniasis that can kill millions of people, so new and effective drugs are urgently needed to combat these infections," said Colin Berry, Ph.D., a researcher involved in the work from the Cardiff School of Biosciences at Cardiff University in Cardiff in the United Kingdom. "The use of existing anti-HIV agents has indicated that there is a potential target in some parasites and by identifying the protein responsible, we hope to exploit this weakness in the parasite to develop new and effective therapeutics to combat these devastating diseases."

Scientists studied yeast that lacked the Ddi 1 protein and found that high levels of proteins were secreted. The addition of the Leishmania Ddi 1 protein returned the yeast to normal low secretion levels until HIV protease inhibitors were added. These inhibitors blocked the ability of Leishmania Ddi 1 to reduce secretions and showed that the Ddi 1 protein interacted with the drugs. Additionally, when researchers used human Ddi 1, they identified drugs that were good at blocking the activity of the Leishmania protein, but which were much weaker against the human equivalent, suggesting that possible side effects in a future drug could be reduced. Study data support the potential use of this class of compounds for leishmaniasis, but do not yet support the use of existing marketed compounds in a clinical context. The potency of the existing compounds indicates that they may be a useful start point for further exploratory chemistry.

"Like HIV, parasitic diseases have been and still are a serious threat to human health world-wide," said Gerald Weissmann, M.D., Editor-in-Chief of The FASEB Journal. "Millions die each year from these maladies and we desperately need new drugs. How fortuitous that agents designed against one killer, HIV, may now be turned against parasitic diseases such as leishmaniasis and malaria."

**Washing with contaminated soap increases bacteria on hands**

People who wash their hands with contaminated soap from bulk-soap-refillable dispensers can increase the number of disease-causing microbes on their hands and may play a role in transmission of bacteria in public settings according to research published in the May issue of the journal *Applied and Environmental Microbiology*. 
"Hand washing with soap and water is a universally accepted practice for reducing the transmission of potentially pathogenic microorganisms. However, liquid soap can become contaminated with bacteria and poses a recognized health risk in health care settings," says Carrie Zapka from GOJO Industries in Akron Ohio, the lead researcher on the study that also included scientists from BioScience Laboratories in Bozeman, Montana and the University of Arizona, Tucson.

Bulk-soap-refillable dispensers, in which new soap is poured into a dispenser, are the predominant soap dispenser type in community settings, such as public restrooms. In contrast to sealed-soap dispensers, which are refilled by inserting a new bag or cartridge of soap, they are prone to bacterial contamination and several outbreaks linked to the use of contaminated soap have already been reported in healthcare settings.

In this study Zapka and her colleagues investigated the health risk associated with the use of bulk-soap-refillable dispensers in a community setting. They found an elementary school where all 14 of the soap dispensers were already contaminated and asked students and staff to wash their hands, measuring bacteria levels before and after handwashing. They found that Gram-negative bacteria on the hands of students and staff increased 26-fold after washing with the contaminated soap.

"This is the first study to quantitatively demonstrate that washing hands with contaminated liquid soap actually increases the number of Gram-negative bacteria on hands. Furthermore, the results directly demonstrate that bacteria from contaminated hands can be transferred to secondary surfaces," says Zapka.

Zapka notes that all the participants' hands were decontaminated after testing by washing with uncontaminated soap followed by hand sanitizer. At the conclusion of the study, all the contaminated soap dispensers were replaced with dispensers using sealed-soap refills. After one year of use, not one of them was found to be contaminated.

A copy of the research article can be found online at [http://aem.asm.org/cgi/content/full/77/9/2898](http://aem.asm.org/cgi/content/full/77/9/2898).

A third of deaths in patients with HIV are attributable to other serious illness present at time of HIV diagnosis

Michael Carter
Published: 03 May 2011

A substantial proportion of the mortality in HIV-positive patients is caused by serious illnesses that were present before diagnosis with HIV, Danish investigators report in the online edition of the *Journal of Acquired Immune Deficiency Syndromes*.

Overall, a third of all deaths were attributable to illnesses that were already present at the time of HIV diagnosis. The study also showed that mortality rates were significantly higher in patients with HIV than in the general Danish population.

The introduction of effective antiretroviral therapy in the late 1990s transformed the prognosis of many HIV-positive patients. Non-AIDS-related diseases are an increasingly important cause of illness and death in patients with HIV, and the burden of such diseases is expected to increase as the HIV-positive population ages.

However, the impact of illnesses acquired by patients before their diagnosis with HIV on prognosis is poorly understood.

Therefore Danish investigators undertook a population-based study involving adult patients who were diagnosed with HIV in the country between 1997 and 2005. These individuals had at least two years of follow-up and each was paired with up to 99 age and sex-matched HIV-negative controls.

Details of co-morbidities were obtained from national registries. The investigators then calculated a Charlson Co-morbidity Index score for each patient and their matched controls. The Charlson Co-morbidity Index includes serious illnesses which are scored from 1 to 3 according to their potential impact on mortality.

Mortality rates were calculated for individuals according to their Charlson Co-morbidity Index score (0, 1, 2, 3 and above).

A total of 1638 patients were diagnosed with HIV during the period of the study, and 195 of these individuals during 9350 person years of follow-up. This provided a mortality rate of 2.09% compared to a rate of just 0.39% in the general Danish population.

Another serious illness was present in 22% of patients at the time of their HIV diagnosis. This included 13% of patients who were co-infected with hepatitis C.
Pre-existing co-morbid conditions significantly increased the risk of death for patients. HIV-positive individuals who had one or more Charlson Co-morbidity Index points had significantly higher mortality rates than HIV-infected patients with no points on the index (mortality rate = 1.84; 95% CI, 1.32-2.57).

The investigators then compared mortality rates between HIV-positive patients and HIV-negative controls according to their Charlson Co-morbidity Index score. In each strata, HIV-positive individuals had a significantly higher mortality rate.

- Score 0: HIV = 1.70 vs. 0.27 per 100 person years.
- Score 1: HIV = 4.37 vs. 1.36 per 100 person years.
- Score 2: HIV = 8.06 vs. 2.44 per 100 person years.
- Score 3 and above: HIV = 10.15 vs. 5.84 per 100 person years.

This excess mortality in patients with HIV was explained by an interaction between HIV and the co-morbid conditions. Compared to patients with no Charlson Co-morbidity Index points, 59% of excess deaths for patients with one point could be attributed to this interaction, 66% of increased mortality for patients with two points, and 34% of excess deaths for patients with three or more points.

Overall, the investigators calculated that 32% of deaths in patients with HIV were due to non-HIV-related causes. Moreover, 45% of total mortality in patients with HIV was due to non-HIV-related causes.

“We found that morbidity acquired before HIV diagnosis was an independent risk factor for death,” comment the investigators.

“Almost half the mortality in persons diagnosed with HIV in a health care setting with free access to HAART [highly active antiretroviral therapy] stemmed from factors unrelated to the HIV disease or associated factors such as toxicity of antiretroviral drugs. Moreover, comorbidity acquired before HIV diagnosis acted synergistically with HIV as a risk factor for death.”

They add, “the considerable burden conferred by diseases acquired prior to HIV diagnosis, found in more than one in five patients in this study, calls for a comprehensive approach to treatment and care. Involvement of a team of medical specialists is clearly needed.”

The investigators suggest that lifestyle and self-care issues could contribute to the high prevalence of pre-existing serious illnesses present in patients at the time of their HIV diagnosis. “Further studies aiming to identify biological as well as sociocultural risk factors for comorbidity are required to increase our understanding of the complex interaction between HIV and diseases acquired before HIV.”

Reference

Researchers Explore Agents that Reduce CD4 Cell Reservoir and Activate Latent HIV

### SUMMARY

A gold compound, auranofin, can kill memory CD4 T-cells that harbor latent HIV, thereby depleting the viral reservoir, according to a recent study. Other researchers used a high-throughput screen to identify compounds that can flush latent virus out of reservoir cells.

**By Liz Highleyman**

Over the past few years a growing body of research has looked at ways to cure HIV, aiming either to completely eradicate the virus or produce a “functional cure” that enables people with HIV to safely stop antiretroviral therapy (ART).

One of the key obstacles to reaching this goal is the fact that HIV genetic material (known as proviral DNA) can integrate itself and remain dormant in a “reservoir” of resting cells—primarily long-lived memory CD4 T-cells—where it is unreachable by current antiretroviral drugs. Researchers have proposed reducing this reservoir by either activating resting cells to "purge" or "flush out" latent virus, or by killing off resting cells that contain integrated viral DNA.

**New Activating Agent**

A study described in the April 15, 2011, advance online edition of the Journal of Biological Chemistry took the first approach, looking for compounds that could activate and purge latent HIV.

Sofiya Micheva-Viteva from Los Alamos National Laboratory and colleagues devised a cell-based system to model HIV latency in the laboratory. They used this model with a high-throughput screen to identify small molecules that could antagonize, or reverse, HIV latency.

They identified a compound dubbed antiviral 6 (AV6) that reproducibly activated latent proviral DNA from different lymphocyte-based laboratory cell lines and from latently infected primary (taken from...
people) resting CD4 T-cells. AV6 did not, however, cause dangerous generalized T-cell proliferation or activation. Furthermore, they also showed that AV6 complemented the ability of a previously known histone deacetylase (HDAC) inhibitor to activate latent HIV.

Based on these results, the investigators concluded, "This is a proof of concept showing that [a high-throughout screen] employing a cell-based model of HIV-1 latency can be utilized to identify new classes of compounds with novel activities that can be used in concert with other persistence antagonists with the aim of viral clearance."

**Auranofin**

As described in the April 18, 2011, advance online edition of AIDS, Mark Lewis, Andrea Savarino, and colleagues tried the second approach, testing whether auranofin (brand name Ridaura)—a gold compound used to treat rheumatoid arthritis—could help deplete the reservoir of T-cells harboring HIV.

The researchers first exposed primary human CD4 T-cells to auranofin in a laboratory study. They found that auranofin promoted cell differentiation, changing the phenotype (markers identifying cell function) of naive, central memory, and transitional memory T-cells. The compound also caused cell death, which was more pronounced for memory cells—the type most likely to contain latent virus.

They next tested whether auranofin could reduce the viral DNA reservoir in a pilot study of 6 macaque monkeys infected with SIV, a primate relative of HIV. At the start of the experiment the macaques had stably suppressed viral load on standard ART consisting of tenofovir (Viread, also in the Truvada and Atripla coformulations), emtricitabine (Emtriva), and the integrase inhibitor raltegravir (Isentress).

Auranofin significantly decreased viral DNA in peripheral blood cells of monkeys on 3-drug ART, though the effect was transient. The gold compound shortened the lifespan and reduced the population size of central memory CD4 T-cells, while not significantly diminishing the naive CD4 T-cell population. Overall CD4 cell counts remained stable.

When ART was intensified by adding ritonavir-boosted darunavir (Prezista), the decrease in SIV DNA was sustained through 11 weeks in auranofin-treated monkeys, but not in a control group on intensified ART alone. Macaques on intensified ART were then treated with the HDAC inhibitor vorinostat at week 10 to see if it could flush out any remaining latent virus. Viral rebound did not occur in monkeys that took auranofin, although it did in control monkeys.

After all treatment was suspended, monkeys that had received auranofin experienced delayed and lower-level viral load rebound after about 7 weeks, compared with less than 2 weeks for control monkeys. One animal maintained a low viral load and stable high CD4 count for nearly a year, Savarino reported.

"These findings represent a first step towards a remission of primate lentiviral infections," the study authors optimistically concluded.

Nevertheless, in a press release describing the research, Savarino cautioned that people with HIV should not yet try this approach using off-label auranofin. "I strongly recommend that people living with HIV/AIDS do not buy the drug from uncontrolled sources such as the e-Bay and start self-treatment outside highly medicalized settings," he stated. 4/29/11

**References**


**Unlocking the metabolic secrets of the microbiome**

The number of bacterial cells living in and on our bodies outnumbers our own cells ten to one. But the identity of all those bugs and just what exactly our relationship to all of them really is remains rather fuzzy. Now, researchers reporting in the May issue of Cell Metabolism, a Cell Press publication, have new evidence showing the metabolic impact of all those microbes in mice, and on their colons in particular.

"We point out one relatively general metabolite in the colon that has profound effects—it does a lot to keep things running smoothly," said Scott Bultman of the University of North Carolina at Chapel Hill. And, he says, that single metabolite, known as butyrate, surely isn’t all that unique. It is but one example of the complex interactions between mammals and their microbial inhabitants among many more yet to be defined.

There were already clues that the microbiome had significant effects on metabolism. For instance, earlier studies showed that "germ-free" mice have to consume 10% more food to maintain their body...
weights compared to normal mice. Bultman’s group wanted to look a little closer at where in the body those metabolic effects might be most important.

They suspected those influences might be stronger in the colon relative to other tissues, where microbes are represented in the greatest numbers. Indeed, that’s exactly what they found.

Those effects were explained by the fact that cells known as colonocytes are literally fueled by bacteria-produced butyrate as their primary energy source, in place of the glucose burned by other cell types. Colonocytes taken from germ-free mice are found in an energy-deprived state, showing lower levels of important metabolic enzymes and the molecular energy currency known as ATP. Those cells manage to survive that way by digesting some of their own components in a process known as autophagy.

When the researchers added butyrate to germ-free colonocytes, it rescued their energy deficit and prevented them from undergoing autophagy, they report.

The findings come at an important time, just as efforts are underway to sequence the genomes of each and every microbe represented in the human microbiome. "As important as the Human Microbiome Project is, it is really just a launching-off point," Bultman said. "A 'parts list' of bacterial genes won’t be enough. We’ll need to know about the metabolites they make and their effects on energy, the immune system, and other functions.

The new insight into the important role of butyrate may also have dietary and clinical implications, the researchers say.

"Dietary factors known as prebiotics promote the growth of certain bacteria at the expense of others and have implications for human health and disease," they wrote. "As our diets have shifted away from fiber and other complex carbohydrates toward processed, simple carbohydrates, the incidences of colorectal cancer and inflammatory bowel diseases such as ulcerative colitis and Crohn's disease have increased. It is possible that increasing butyrate levels in the lumen and in colonocytes could help reverse this trend. In fact, butyrate enema therapy has been shown to ameliorate the inflammation associated with colitis in mouse models and in human clinical trials."

**Receptor for Ebola Virus Identified**

ScienceDaily (May 3, 2011) — A team of researchers has identified a cellular protein that acts as a receptor for Ebola virus and Marburg virus. Furthermore, the team showed that an antibody, which binds to the receptor protein, is able to block infection by both viruses.

"This is the first receptor identified for Ebola and Marburg viruses," said Wendy Maury, Ph.D., associate professor of microbiology at the University of Iowa Roy J. and Lucille A. Carver College of Medicine and senior study author. "That’s important because if you can identify and understand the first step in infection — how the virus enters cells — then perhaps you can prevent the infection by nipping it in the bud."

Ebola and Marburg viruses cause hemorrhagic fever in humans and other primates. For some strains, infection can lead to death in 50 to 90 percent of cases, and there is no cure or effective treatment. The findings are published online the week of May 2 in the Proceedings of the National Academy of Sciences Early Edition.

Maury led a multidisciplinary team that included colleagues from four UI departments as well as collaborators at the National Institute of Dental and Craniofacial Research (NIDCR) in Bethesda, Md., University of Texas Medical Branch in Galveston, Texas, and Biogen Idec, in Cambridge, Mass.

The researchers used a new bioinformatics-based approach, developed by John Chiorini at NIDCR, to identify a protein called TIM-1 as a receptor for Ebola and Marburg viruses. Subsequent experiments proved that both Ebola and Marburg viruses use TIM-1 as a receptor for infecting cells.
The study also showed that TIM-1 protein is widely expressed on epithelial cells that line various tissues in the body including mucosal surfaces of the airways and in the eyes. Maury noted that these locations are consistent with some of the ways the Ebola virus is thought to be transmitted—inhalation of aerosolized droplets and hand-to-eye contact.

A further collaboration with Paul Rennert, Ph.D., at Biogen Idec, a biotech company based in Cambridge, Mass., provided the team with antibodies targeted to TIM-1 and the team found that one of these antibodies, ARD5, very effectively blocks Ebola and Marburg virus entry into cells.

Finally, work performed by Robert Davey, Ph.D., in a BSL-4 lab (the highest level of biocontainment) at University of Texas Medical Branch verified that the ARD5 antibody blocks infection by infectious Zaire Ebola Virus in cells that express the TIM-1 protein. The results suggest that being able to block Ebola’s entry into epithelial cells, perhaps with a human-compatible version of the ARD5 antibody, might provide a way to prevent initial infection and potentially limit the spread of the disease during an outbreak.

Importantly, the study found that TIM-1 protein is not expressed on all the cell types that are infected by Ebola and Marburg. "It’s clear that there are other receptors for Ebola because while TIM-1 is found on a number of epithelial cells in the body, it is not found on some important cell types that are infected by Ebola," Maury said. "Ultimately, epithelial cells are not as important a target for the virus as some other cell types, but they may be the first entry point for Ebola, so they may provide a conduit that allows Ebola access to those other cells within the body."

Journal Reference:

Lesser-Known Escherichia Coli Types Targeted in Food Safety Research

ScienceDaily (May 2, 2011) — Almost everyone knows about *Escherichia coli* O157:H7, the culprit behind many headline-making outbreaks of foodborne illness in the United States. But the lesser-known relatives of this pathogenic microbe are increasingly of concern to food safety scientists.

That’s according to U.S. Department of Agriculture (USDA) microbiologist and research leader Pina M. Fratamico. Researchers such as Fratamico, along with food safety regulators, public health officials and food producers in the United States and abroad, want to know more about these less-studied pathogens.

In the past few years, a half-dozen of these emerging *E. coli* species, also called "serogroups," have come to be known among food safety specialists as "the Big Six," namely *E. coli* O26, O45, O103, O111, O121, and O145.

Fratamico and her colleagues are sorting out "who’s who" among these related pathogens so that the microbes can be identified and detected quickly and reliably. The researchers are doing that by uncovering telltale clues in the microbes’ genetic makeup.

Building upon this work, Fratamico and her Agricultural Research Service (ARS), university, and industry collaborators have developed gene-based PCR (polymerase chain reaction) assays to help identify and detect six newly important *Escherichia coli* species that are close relatives of *E. coli* O157:H7 (shown here at about 16,000 times normal size). (Credit: Peter Cooke, Colorization by Stephen Ausmus)

Analyses of test results might help researchers determine whether certain strains of Big Six *E. coli* species cause more illness than *E. coli* O157:H7 does, and if so, why.
By Megan Scudellari

**Power Failure (long)**

*Does mitochondrial dysfunction lie at the heart of common, complex diseases like cancer and autism?*

Kevin Hand

Mitochondria are tiny. A single human cell can contain hundreds to thousands of these potato-shaped organelles, depending on the tissue type. They power the biochemical reactions in our cells through the production of adenosine triphosphate (ATP).

These oft-overlooked furnaces, not studied in earnest until the 1970s, are now the subject of intense scrutiny for their potentially central role in common, complex diseases. They may be, scientists say, pivotal to the etiology of diseases such as cancer and Alzheimer’s, epidemics against which researchers and companies have spent billions of dollars but made arguably little progress.

But not everyone agrees with the mitochondrial hypothesis. Complex diseases are simply that, some researchers argue—complex. While mitochondria are essential to human physiology, there has not been sufficient evidence to prove that mitochondrial dysfunction plays a causative role in complex diseases. When it is implicated, debate ensues over whether errors in energy production contribute to disease pathology or are simply a consequence of it. “The question remains, as it should, how often [are mitochondria] a major player?” asks Marvin Natowicz, a clinician specializing in autism and mitochondrial disease at the Cleveland Clinic in Ohio.

It doesn’t help that studies of human mitochondrial function are invasive, costly, and lengthy. But over the last five years, a growing number of papers by researchers around the world have implicated dysfunctional mitochondria in many elusive diseases, including Parkinson’s, autism, and aging. And leading the charge is an unlikely champion, a respected and renowned member of the National Academy of Sciences who is simultaneously a self-proclaimed radical and zealot: a man about whom colleagues hesitate to comment, a maverick known for mounting a soapbox to hold forth on the “vital force,” Eastern medicine, and E=mc².

On a brisk February morning, Douglas Wallace walks through the halls of the Center for Mitochondrial and Epigenomic Medicine, a new research center at the Children’s Hospital of Philadelphia, spouting philosophy. “Every one of the diseases we can’t solve is absolutely logical if we put energy at the center,” he says. “I believed that in 1970 and I believe it now.”

A short, cheery man with gold-rimmed glasses, a yellow and green paisley tie and oversize pants held up by blue suspenders, Wallace is a founder of the field of human mitochondrial genetics. As a researcher he has published over 230 papers and is consulted by clinicians about some of the world’s trickiest diseases. But he is also a man on a mission to convince the scientific establishment that they’ve got it all wrong.

Medicine fails to solve many of today’s common, complex diseases, Wallace asserts, because the fundamental paradigm is wrong: the medical establishment has spent far too long focusing on anatomy and ignoring energy—specifically, mitochondria.

It has been his tune for more than 30 years, though it’s often fallen on deaf ears in the scientific community. But today, the idea that energy deficiency plays a major role in human disease appears to be gaining momentum, as more and more papers link mitochondrial dysfunction to disease. The shift has prompted Children’s Hospital to put their money behind his research, and has caused many in the community to wonder: Is Doug Wallace crazy? Or is he right?

**A Pandora’s box of mutations**

Mitochondria generate energy in the form of ATP by combining nutrients and oxygen in a chemical reaction called oxidative phosphorylation (OXPHOS). The mitochondrion is hypothesized to have originated as a bacterium engulfed by another cell some two billion years ago. Mitochondrial DNA (mtDNA) is circular, with 37 genes, 13 of which encode subunits of enzymes involved in OXPHOS and so are analogous to the wiring diagram for a power plant. (See “Mitochondria at Work” below.) More than a thousand additional genes in the nucleus of the cell (nDNA) are involved in the maintenance, growth, and replication of mitochondria, and around 80 of those nuclear genes code for proteins involved directly in OXPHOS. While nDNA is inherited from both the mother and the father, in 1980 Wallace demonstrated that human mtDNA is inherited only from the mother.

In 1988, Wallace took our understanding of mtDNA a step further: He discovered, for the first time, that mutations in mtDNA cause disease. He identified a point mutation in a protein subunit that results in Leber’s hereditary optic neuropathy, a form of midlife blindness. Shortly after, Wallace identified an
mtDNA mutation associated with a form of progressive epilepsy accompanied by muscle weakness. It was his first glimpse into a Pandora’s box of diseases caused by mutations in that small, circular DNA. Today more than 400 point mutations, as well as innumerable mtDNA rearrangements, are linked to heart disease, epilepsy, deafness, blindness, anemia, and more. In addition, mutations in nDNA genes can cause mitochondrial disease, as can combinations of nDNA and mtDNA mutations.

“At the moment, there are about 120 different [mitochondrial] genetic disorders, and there are probably as many again to be discovered,” says David Thorburn, head of mitochondrial research at the Murdoch Childrens Research Institute in Victoria, Australia. A primary mitochondrial disease—one caused by a mutation in mtDNA—is not easy to diagnose and often involves many organ systems, including heart, brain, muscle, and gastrointestinal tract. “We used to say, if three or more systems are involved, think mitochondria,” says Marni Falk, a pediatrician at Children’s Hospital of Philadelphia and a leading mitochondrial researcher. In addition to the production of ATP, mitochondria regulate calcium control in the cell and guide cell death. “They’re like the conductor of the orchestra,” says Falk. “When they’re not working, all is disrupted.”

Sadly, there is a dearth of therapies for well over 95 percent of primary mitochondrial disease cases. “The treatments we hoped would prove effective have been really disappointing,” says Marc Yudkoff, chief of child development and rehabilitation medicine at Children’s Hospital. “The area of mitochondrial disease has become our most pressing concern.” Children’s Hospital is a hub of research into primary mitochondrial diseases and treatments for their victims, with hundreds of cases referred each year—and “the pace is increasing,” says Falk. In 2007, she established a mitochondrial research group at the hospital, bringing together over 175 specialists in numerous fields—from endocrinology to anesthesiology to hematology to surgery—to spark collaborations to identify new biomarkers and treatments for such diseases.

But beyond the need for therapies and research into primary mitochondrial diseases, Wallace believes there is an even larger, unrecognized chasm in the medical community. Over the last fifty years, despite billions of dollars in funding, the medical community has failed to discover causes or treatments for many common, complex diseases: heart disease, Alzheimer’s, autism, and more. Wallace attributes that continuing failure to the fact that clinicians and researchers base medical training and treatments on anatomy. If someone has a headache, for example, doctors look to the head. If the patient has chest pain, a clinician examines the heart or lungs. Doctors are taught organ-specific medicine in school, and the NIH still organizes its research centers based largely on organ systems: the National Eye Institute, the National Heart, Blood, and Lung Institute, and the National Institute of Diabetes and Digestive and Kidney Diseases, for example. But life is structure plus energy, argues Wallace, and we’ve been missing the second half of that equation.

It is “self-evident” in some ways, says Yudkoff. Disease is caused by a loss of organization—by entropy—which is essentially a loss of energy. “On a basic physical and chemical level, it’s not arguable,” he says. Thorburn adds, “The whole area is fascinating and plausible. [Wallace] has done some pioneering work. He sells it very hard, but people are very much interested in the ideas and following up on them.”

To Wallace, looking at complex diseases through the lens of mitochondria makes everything clearer. “I’m not saying anything done before isn’t good. It’s just not complete,” says Wallace. Especially, he believes, when trying to understand the elusive link between disease, genetics, and the environment.
Genome-wide association studies (GWAS), a popular tool to find genetic variations associated with a particular disease, have for the most part had limited success. Their failures are often blamed on confounding environmental factors. Mitochondria, notes Wallace, are that missing factor: they act as a direct link between our genes and the environment, taking in calories and oxygen (products of the environment), and producing ATP and acetyl coenzyme A, two molecules involved in the regulation of most biochemical reactions, including gene expression. In addition, during OXPHOS, mitochondria generate reactive oxygen species (ROS), the smoke from the furnace. At low levels, the ROS provide a critical signaling system from the mitochondrion to the cytosol and nucleus. However, at high levels, these free radicals cause significant damage to the cell and organelles, especially to the mitochondria themselves. Consequently, mtDNA has a much higher mutation rate than nuclear DNA. Thus, the most common genetic changes caused by the environment are mutations in mtDNA, says Wallace. These inheritable changes, plus mitochondrial regulation of nuclear DNA gene expression by ATP and acetyl coenzyme A, are the major factors contributing to predisposition to the common diseases, argues Wallace. Yet GWAS only analyze nDNA, not mtDNA. “GWAS are wonderful,” says Wallace. “The problem is they don’t include energetics.”

Today, Wallace finally has the backing of a major research hospital to explore these ideas and more. In 2009, while visiting Children’s Hospital, Wallace spoke with Yudkoff about his desire to start a center focused on the role of mitochondria in common, complex diseases. “It was a bit like Einstein asking if he’s welcome in a physics department,” says Yudkoff. “There’s arguably no one alive with more impeccable credentials in the field.”

The Center for Mitochondrial and Epigenomic Medicine (CMEM) opened July 2010, with 19 of Wallace’s staff from his previous post at the University of California, Irvine, joining him. In addition to staff, Wallace brought his mice. Over decades, he has created numerous mouse models in an effort to
prove a direct cause-and-effect relationship between mitochondrial defects and common diseases. In 1997, for example, he created a mouse deficient in Ant1, a nuclear-encoded protein involved in ATP synthesis, loss of which produces debilitating heart and muscle disease. He has also created mice harboring mtDNAs with a single base change in the mtDNA COI gene. These animals develop heart and muscle disease as well as other symptoms, demonstrating that a single mtDNA mutation is sufficient to cause degenerative disease. Today, Wallace has over 3,000 mice with different mitochondrial defects serving as models for diseases including diabetes, hypertension, blindness, and neurological problems.

The Center, now stocked with mice and staff, could not have opened at a more opportune time. Today there is a “renaissance” of researchers considering the role of energy and mitochondria in common disease, says Falk. “In the last decade, there’s been an explosion of research,” she says. Still, while studies of nuclear DNA implicate new genes in complex diseases every day, mtDNA studies are far fewer and more difficult to perform, typically requiring an invasive muscle biopsy and an analysis of the percentage of mutated mitochondria within a cell or population of cells. To catch the attention of the medical community, every last scrap of research will be needed. Extraordinary claims, as they say, require extraordinary evidence.

**Altered metabolism in complex diseases**

In 2005, a population-based study at a school in Portugal demonstrated that seven percent of autistic children studied had disturbances in mitochondrial energy metabolism. It raised the question that mitochondria certainly play a role, says Gasser, but for the more common, sporadic cases of Parkinson’s, “the primary defect lies somewhere else.”

There is also budding evidence for the role of mitochondrial dysfunction in other common neurodegenerative diseases. Recent studies suggest that amyloid-beta, the chief component of the characteristic plaque of Alzheimer’s disease, progressively accumulates within mitochondria, acting as a direct toxin. In addition, defects in OXPHOS, including mutations in mtDNA, have been frequently associated with the disease. And a recent study from Newcastle University found that mtDNA deletions may also be an important contributor to multiple sclerosis.

In 2005, a population-based study at a school in Portugal demonstrated that seven percent of autistic children studied had disturbances in mitochondrial energy metabolism. “It raised the question that disturbances of mitochondrial function might be a reasonably common finding in persons with autism,” says Natowicz of the Cleveland Clinic. Yet researchers are divided over the degree to which mitochondrial dysfunction actually contributes to the autistic phenotype, and over whether people with OXPHOS disorders are a clinically distinct population of autistic individuals or no different from most who suffer from autism. More large population-based studies might answer that question, says Natowicz, but they have yet to be done. “This is a central question [in autism] that needs much more attention,” he concludes.

**Genome-wide association studies are wonderful. The problem is they don’t include energetics.** — Douglas Wallace

But nowhere is the study of altered metabolism more popular than in cancer research. Researchers have long observed that metabolism in tumors is different from metabolism in noncancerous cells, possibly because cancer cells must accommodate the increased metabolic demands of rapid cell proliferation. The study of metabolism in cancer cells has “exploded” over the last five years, says Eyal
Gottlieb, a researcher at the Beatson Institute for Cancer Research in Glasgow, Scotland. There are hundreds of papers describing mitochondrial DNA mutations in cancer, including Wallace’s own work identifying mtDNA mutations in prostate cancer. But alterations in mitochondrial DNA and function could be a consequence of a cancerous phenotype, rather than the cause. There are some instances where scientists have demonstrated a direct causal role of mitochondria dysfunction in cancer, but such cases are, at the moment, “the exception to the rule,” says Gottlieb. Still, he adds, “There is a link there, even if we don’t fully understand it.”

For now, the role of mitochondria in common diseases continues to be investigated in numerous studies. Still, the majority of clinicians in all of these fields—even in Parkinson’s, where the evidence seems strongest—have not embraced Wallace’s paradigm-shifting theory.

**A new concept of medicine**
Wallace walks down a long, empty corridor. To the right, row after row of sparkling lab benches stand empty and waiting. Today, only twenty-one people fill one of the four lab bays that will make up the new center, but already the team is tackling projects in metabolic syndrome, cancer, heart disease, and aging. Wallace has plans to hire more new faculty plus support staff this year.

He reaches the end of the corridor and turns, walking into one of the center’s new conference rooms, which appropriately overlooks a silent power plant, silhouetted against the cold Philadelphia sunset. His voice has grown hoarse. He settles back into a chair. In the end, Wallace, whose mother had Alzheimer’s and whose son is autistic, isn’t out to criticize his colleagues, but to save lives. “I don’t know how long it’s going to take for people to see this is relevant,” he says with a sigh, looking out at the quiet plant below. “We now have a mitochondrial, energy-based concept of medicine, which beautifully explains in a simple way all the previous inexplicable problems. Things are only complex when we don’t understand them.”

**METHODS: ID'ING DISEASE-RELATED MUTATIONS IN MITOCONDRIONAL DNA**
In the effort to identify mitochondrial DNA (mtDNA) mutations associated with human disease, a major hurdle has been the fact that there is no “normal” mtDNA sequence. As Wallace and colleagues discovered beginning in the 1980s, human populations around the world have high levels of variation in mtDNA, which can be sorted into distinct haplogroups, or branches, reflecting their geographic origins.

Lucy Reading-Ikkanda (map); Source: Copyright 2002 © Mitomap.org

mtDNA in modern humans dates back to Africa some 150,000 to 200,000 years ago. Based on samples of mtDNA collected around the world over decades, Wallace’s team has mapped this remarkable correlation between mtDNA variation and place of origin: as humans spread around the globe out of Africa, populations acquired adaptive mutations allowing them to thrive in different climates. (See map at left: letters denote mtDNA lineages.) In cold regions, for example, lineages acquired mtDNA mutations that resulted in a less-efficient oxidative phosphorylation system, with decreased ATP production, but increased heat production.

This high degree of mtDNA variation puts clinicians in a quandary. How can one identify which variations cause disease and which are simply the result of a person’s geographic origins? For example, sequencing the mtDNA of more than 500 patients known to suffer from mitochondrial cardiomyopathy resulted in over 200 different sequence variants—far too many to identify a culprit.

To resolve the issue, Wallace and his team recently designed an automated analysis system they call MITOMASTER to compare the mtDNA sequences of patients with a database of thousands of mtDNA haplogroups. Analyzing the mtDNA sequences of 29 Italian patients with mitochondrial heart disease, the researchers identified 593 mtDNA variants, but found that 98 percent of them were haplogroup-associated. Six mutations, however, were novel and not associated with a haplogroup, suggesting they were possible disease contributors (Eur J Hum Genet. 19:200-07, 2011). The approach demonstrates that clinicians shouldn’t be analyzing individual mtDNA sequences in isolation, and that automated systems can help researchers ferret out links between mtDNA mutations and disease pathology.
According to DSM IV, autism is a disorder, not a disease.

If you are going to write about autism please get it right. We do not need any more confusion in the area.

Perhaps even more importantly I want to point out that there is sometimes a pharmacological (rather than genetic) focus of this lab is not merely on mitochondrial DNA mutations. Surely these folks know that most of the encoded. It is quite likely that many “mitochondrial” dysfunctions are due to problems with nuclear-encoded gene products, and mutations in those genes should therefore also be sought out in conjunction with various hereditary medical conditions.

Perhaps even more importantly I want to point out that there is sometimes a pharmacological (rather than genetic) basis for some mitochondrial dysfunctions. For example, the mechanism of action of statins is to inhibit the enzyme that synthesizes mevalonic acid, which is a key metabolic precursor to cholesterol. However, mevalonate is also a key metabolic precursor of two other critical products: dolichol and coenzyme Q. Statins are therefore used at dosages that only partially inhibit total enzyme activity. However, the enzyme that takes mevalonate down the “dolichol” pathway has much higher affinity than the enzyme that takes it down the “CoQ” pathway, and as a result it is quite likely that some people will develop CoQ insufficiency (but probably not dolichol deficiency) due to statins. This is the likeliest cause of statin-associated leg muscle pain (since exogenous CoQ administration usually relieves that pain), and CoQ insufficiency should also be suspected as a possible cause for other side effects (liver, kidney, heart muscle) that are associated with statins. There are certainly other pharmacological agents in therapeutic use today that impact either directly or indirectly on mitochondrial function. There’s a wealth of exploration that needs to be done here.

All of which is to say that this is a stimulating article, and there’s a lot of work that should be done in this area.

Autism: disorder not disease
by Neil Toner, Comment posted 2011-05-03 10:50:57
According to DSM IV, autism is a disorder, not a disease.

If you are going to write about autism please get it right. We do not need any more confusion in the area than we already have.

References:
An outspoken health expert, known for exposing the SARS cover-up in 2003, claims a mysterious infectious condition dubbed "negative AIDS" is more than a mental health problem, citing an independent study he led.

Zhong Nanshan told the Guangzhou-based New Express Daily: "The condition was not simply caused by mental problems," adding more information will be publicized soon at a coming seminar.

He also revealed that most of the alleged sufferers involved in his study suffered reactive arthritis. His remarks appear to contradict the findings of a government investigation led by the Ministry of Health.

In mid April, the ministry dismissed media reports on the existence of the so called "negative AIDS" virus citing results from their probe.

Wu Zunyou, an AIDS expert with Chinese Center for Disease Control and Prevention said no new virus have been found among the alleged sufferers and they were most likely just suffering from a mental health problem called AIDS phobia.

Starting in 2009, media reports stated that sufferers display AIDS-like symptoms, including swollen lymph glands and bleeding under the skin, but repeatedly test negative for HIV.

In response, Zeng Guang, chief epidemiologist at the Chinese Center for Disease Control and Prevention, held the country's first government-initiated study of the issue, which involved experts in infectious diseases and mental health professionals.

A total of 59 sufferers were interviewed and examined, the report said. Many of the people with the condition were engaging in high-risk behavior and had a strong fear of contracting AIDS/HIV, according to Zeng.

"The conclusion was reached that there was no such thing as a new AIDS-like virus or so-called negative AIDS," he said.

Is There a Future for HIV-Infected Patients in "Deep Salvage"?

By Nelson Vergel, B.S.Ch.E., M.B.A.
May 3, 2011
"Only patients who do not take their medications as prescribed have multidrug resistance."
"Deep salvage patients no longer exist. The ones in that situation are already dead or have responded to the latest HIV antiretrovirals."
"Even if we give expanded access to multiple investigational agents to patients in salvage therapy, it will be a waste since most of these patients have adherence problems."
"It is too expensive and cumbersome for my clinic to provide expanded access."
"My institution no longer participates in expanded access due to costs and manpower problems."

These are statements that I have heard in different meetings that I have attended in the recent past to discuss access and research issues in HIV. Some of these statements are very hard for me to hear, since I am one of these "difficult patients" who have "failed" most commercially available medications—despite the fact that I, like many of my peers, am certainly not a patient who lacks perfect adherence.

Most of us built resistance as we joined study after study that exposed us to functional monotherapy. In fact, I consider many of us who have been struggling with multiple drug resistance to be wounded soldiers from a time when we were recruited into studies we joined out of desperation to access a new drug. Even if we seem invisible due to our lower numbers, we are still here—and we absolutely hate to be discounted as disposable in the current era of largely successful HIV treatment.

It is my opinion, and that of several clinicians that I have worked with, that it is the pharmaceutical industry's duty to provide access to multiple investigational drugs so that so-called "salvage patients," such as myself, can finally construct a regimen that may help us join the population of virologically controlled patients.

We all know that the management of resistant HIV disease has improved dramatically with the approval of a number of highly effective antiretroviral drugs, including darunavir (TMC114, Prezista), etravirine (TCI255, Intelen), maraviroc (Selzentry, Celsentri) and raltegravir (Isentress). Among this recent generation of antiretroviral drugs, perhaps the most promising is raltegravir, the first clinically available inhibitor of HIV integrase. When used in combination with other active drugs, raltegravir has proven to be very potent, well tolerated and highly effective. In phase 2 and 3 clinical trials, the vast
The majority of patients who were able to combine raltegravir with at least one other active drug achieved durable viral suppression. (Comparable efficacy has been seen in patients who received darunavir, etravinire or maraviroc with at least one other effective agent.)

Despite the impressive effectiveness of these drugs in clinical trials, a subset of patients has exhibited virologic failure while on these drugs. Most failures likely occurred because of the inability to construct a regimen that contained two to three fully effective agents. Adverse events, drug-drug interactions and non-adherence also likely contributed to the inability of some patients on these drugs to achieve durable viral suppression. As a consequence of these factors, the failure rates in the recent phase 3 studies—DUET (etravirine and darunavir), MOTIVATE (maraviroc) and BENCHMRK (raltegravir)—were in the 27% to 40% range.

The picture gets less encouraging when looking at longer-term data. As shown in the following figure, a longer-term study generated from following patients using raltegravir for 144 weeks showed failure rates of 40% to 56% even in patients with one or more active agents in their background therapy.

144-Week Efficacy of Raltegravir in Treatment-Experienced Patients
(J.M. Gatell et al, IDSA 2009)

<table>
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<tr>
<th>Baseline GSS</th>
<th>n/N</th>
<th>% with HIV RNA &lt; 50 copies/mL (95% CI)</th>
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<tr>
<td>3 or more</td>
<td>3/5</td>
<td>60 (15, 95)</td>
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But I guess these patients disappear into the dark, since many physicians do not seem to know who they are. It is assumed that many of the patients who failed these recent studies were subsequently unable to construct a suppressive regimen, although the long-term outcomes of those failing these clinical trials are unknown.

The prevalence of multi-regimen failure in clinical practice is also unknown. Steven Deeks, M.D., and colleagues at the University of California San Francisco/San Francisco General Hospital have an ongoing observational cohort of patients who have developed drug-resistant HIV (the SCOPE cohort). Most of these patients have been able to construct a fully suppressive regimen but are currently doing well clinically.

However, of the original 300 SCOPE patients, approximately 40 now have evidence of having failed all six therapeutic drug classes. These 40 patients have a genotypic sensitivity score (GSS) of either zero or one, and they have no clear options for suppressing HIV replication. Many have advanced disease (with a CD4+ cell count of less than 100 cells/mm³) and hence may not be able to "wait" for the development and approval of multiple new options.
In an informal online survey I made with the help of a team of investigators and activists, which was presented in a meeting with the U.S. Food and Drug Administration (FDA), 83 physicians around the country reported having a total of 252 patients with a GSS of zero or one.

<table>
<thead>
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<th>Number of patients with GSS= 0 or 1</th>
<th>Response Percent</th>
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<td>More than four? (please specify)*</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Answered question</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Skipped question</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

*There were 12 physicians who wrote “more than four,” comprising 123 patients.

Total # of patients = 252

The most surprising finding was the wide geographical distribution of these patients. Physicians from 47 U.S. cities and towns reported treating them. Although the larger cities had the most patients with a low GSS, many patients lived in small towns that are far from research sites or large practices that are more equipped to handle the needed paperwork to apply for expanded access or single-patient emergency drug access programs.
Much of the expanded access program documentation and nurse/physician time is not reimbursable or paid for by studies, so most doctors participating in these programs are doing so from the goodness of their hearts. Many large medical schools and clinics have stopped providing expanded access help to their patients entirely.

The following chart outlines some of the reasons reported by survey participants for not applying for early access to investigational drugs for their patients. The most common reason was that they simply did not have the administrative support they needed to handle the required paperwork. Many also expressed frustration with an application process they felt was too complex.
Given that patients who are unable to construct a background regimen often fail therapy, the FDA and other interested groups have advocated that future clinical trials only enroll patients whose background regimen has a GSS or phenotypic susceptibility score greater than or equal to one. Although this is an ethically sound recommendation, one unfortunate consequence is that those patients who have now progressed to multi-regimen failure won't be able to access experimental drugs via clinical trials.

Unfortunately, the HIV drug pipeline in 2011 is a lot more limited than it has been in the past due to many factors, including the relatively small size of the U.S. market, drug development costs, and the difficulty finding treatment-experienced patients with one or more active agents in their background therapy. Some drugs have already been abandoned due to these issues, as shown by this table.
Thankfully, the FDA has proposed a new trial design concept that will facilitate the development of medications for treatment-experienced patients, which may encourage pharmaceutical companies not to abandon HIV drug development. For more information about this novel trial design concept, refer to a presentation given by Jeffrey Murray, M.D., M.P.H., from the FDA at a recent meeting sponsored by the Forum for Collaborative HIV Research.

However, even with these efforts, the possibility of constructing a regimen with three active agents for the salvage population within the next four years is low, which will diminish the chances for survival in those with lower CD4+ cell counts.

I've laid out a grim scenario in this blog post, but in my next post, I'll discuss a potential silver lining: a program in the works that I hope will greatly expand options for deep salvage patients in need of access to investigational agents.

**FDA Cracks Down on Sale of Bogus STD Cures**

*Los Angeles Times*, (05.03.2011) Marni Jameson, Orlando Sentinel

In a joint effort announced Tuesday, the Food and Drug Administration and the Federal Trade Commission (FTC) said they had ordered 11 companies to stop selling fake STD cures or face criminal action. The targeted products include Medavir, Herpaflor, Viruxo, C-Cure, and Never An Outbreak. The companies warned by FDA claim their products treat and prevent the spread of STDs such as HIV/AIDS, herpes, chlamydia, gonorrhea, syphilis, and genital warts.

“These companies need to stop making these claims and stop selling these products or face regulatory action, including seizure and injunction and criminal prosecution,” said Howard Sklamberg, FDA’s director of enforcement. “We need to warn consumers of these fraudulent claims and make them aware that these products are out there, and they don’t do what they say. This is not only a threat to individual health, but also to general public health.”

Officials reminded the public that the only medications proven to treat the STDs referenced in the products’ advertising are available by prescription from a licensed medical practitioner. No nonprescription product has been shown to prevent or treat these conditions; persons who use such products may not seek effective medical treatment and may continue spreading the infections.
Shame and fear may cause some people to seek STD treatment from the Internet rather than a medical provider, said Dr. Jeffrey Engel, health director of the North Carolina Department of Health and Human Services. Concern over the reportable nature of most STDs and the resulting partner-notification procedures also plays a part, he said.

The two federal agencies handled the matter jointly because the FDA oversees labeling and product claims, while the FTC regulates advertising.

Consumers can report any problems relating to these products to FDA’s MedWatch program; telephone 800-332-1088 or visit www.fda.gov/medwatch/report.htm. For more information, visit http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm253619.htm.

HIV-Positive Former Inmates Face New Obstacles in Society

According to the US Department of Justice, about 1.5 percent of state and federal prisoners are HIV-positive. Though some inmates engage in high-risk behaviors behind bars—including unprotected sex, injection drug use, and tattooing—data do not support the assumption that former inmates play a central role in the black community’s high HIV rates, said Joseph B. Richardson Jr., PhD, an assistant professor of African-American studies at the University of Maryland. In fact, infection risk may increase once inmates leave prison and return to high-prevalence communities, he said.

Many returning inmates assume their partner has been celibate, which may not be the case, Richardson said. In addition, new partners the former prisoners meet “can possibly be engaging in unprotected, high-risk sex.”

Precious Jackson, a women’s health educator at the Center for Health Justice in Los Angeles, said couples need to communicate about sex and the risk of HIV after a partner has been incarcerated. She recommends that both parties get tested for HIV.

For HIV-positive former inmates, accessing medication, stable housing, and routine medical care are essential, said Lena Asmar, director of clinical and social support services at AIDS Action Committee of Massachusetts. “What often makes people’s health decline after they get out of incarceration is not having stability to take their medication,” she said.

Asmar suggests the following steps for HIV-positive people leaving prison:

- *Find an advocate: Local AIDS service organizations can provide information about programs and services that can help.
- *Explore local hospitals’ offerings: “Look for one that does infectious-disease work and has providers that are not judgmental and know about HIV.”
- *Get emotional assistance: Feeling isolated after returning home from prison is common. A local HIV/AIDS support group can help inmates better handle the challenges they face.

Tutu Says South Africa No Longer Embarrassed over AIDS

South Africa, which suffered through years of official AIDS denialism, need not be ashamed of its current response to the epidemic, Desmond Tutu said Tuesday. The former Anglican archbishop of Cape Town, now retired, spoke at a UN conference dedicated to enlisting a new generation of activists to combat AIDS.

“For many years, we were embarrassed in international gatherings for what we were not doing in fighting AIDS. We therefore thank the Minister of Health Aaron Motsoaledi for the change in policy,” Tutu said. The campaign led by Motsoaledi was launched in 2009 by President Jacob Zuma; it followed years of ineffective action by the previous health minister, who publicly questioned the link between HIV and AIDS.

“We are definitely joining hands with the rest of the world in the fight against HIV/AIDS,” Motsoaledi said at the conference. “I think we will win.”

Those attending included Tung Bui, of the Vietnamese group Youth Lead. “We are ready to make a difference in the lives of many who have been infected, while preventing future infections,” Bui said. Tutu responded, “It is a very rare privilege and honor for us, the older ones, to say we are passing the baton to you, the young, to carry on with the fight against this pandemic.”

The conference was held on Robben Island, near Cape Town, where the prison that once housed future President Nelson Mandela and other anti-apartheid activists has been converted to a museum.
HIV Drug Could Prevent ‘Cervical Cancer by Killing Off Virus that Causes Disease’

Daily Mail (London), (05.03.2011)

The HIV drug lopinavir is selectively toxic to human papillomavirus-positive cervical cells, a new study suggests. About 3,000 UK women are diagnosed with cervical cancer annually, mostly due to HPV infection by high-risk strains, which have also been linked to oral cancers.

Previous laboratory cell cultures found the protease inhibitor killed HPV-infected cells but left healthy cells relatively unharmed. In the new study, Dr. Ian Hampson, of the University of Manchester, and Canadian colleagues concluded that lopinavir’s toxicity is related to its ability to block viral proteasome activation and induce an up-regulation of the antiviral protein Ribonuclease L.

“Lopinavir kills these HPV-infected cells by reactivating a well-known antiviral system that is suppressed by HPV,” Hampson said. “This is a very significant finding as these cells are not cancer cells but are the closest thing to being like the cells found in a precancerous HPV infection of the cervix,” Hampson said.

However, an effective treatment would need to be administered at a dosage 10-15 times that taken by HIV patients. That could require a cream or vaginal insert rather than oral formulation, said Hampson.

“These results are very exciting since they show that the drug not only preferentially kills HPV-infected non-cancerous cells by reactivating known antiviral defense systems, it is also much less toxic to normal non-HPV-infected cells,” said study co-author Dr. Lynne Hampson. “Our latest findings provide very strong evidence to support a clinical trial using topical application of this drug to treat HPV infections of the cervix.”

The study, “Lopinavir Up-Regulates Expression of the Antiviral Protein Ribonuclease L in Human Papillomavirus-Positive Cervical Carcinoma Cells,” was published online ahead of the print edition of Antiviral Therapy (2011; doi:10.3851/IMP1786).

New mitochondrial control mechanism discovered

[PRESS RELEASE 4 May 2011] Scientists have discovered a new component of mitochondria that plays a key part in their function. The discovery, which is presented in the journal Cell Metabolism, is of potential significance to our understanding of both inherited and age-related diseases.

Mitochondria are normally called the cell’s power plants since they convert the energy in our food into a form that the body can use. To work properly, the mitochondria have to form new proteins, which they do in their ribosomes.

A group of researchers at Karolinska Institutet and the Max Planck Institute for Biology of Ageing has discovered that a protein called MTERF4 combines with another protein called NSUN4 to form a complex that controls the formation and function of the mitochondrial ribosomes. In mice lacking MTERF4 no functional ribosomes are formed, leading to a reduction in energy production.

"Reduced mitochondrial function is involved in several inherited diseases, normal ageing and age-related diseases," says Professor Nils Göran Larsson, who co-led the study with Professor Claes Gustafsson. "Fundamental knowledge of how mitochondrial function is regulated can therefore be of great clinical significance in the future."

The research group previously discovered similar regulation mechanisms in the mitochondria that were found to be related to the development of diabetes.

Publication:
Yolanda Cámara, Jorge Asin-Cayuela, Chan Bae Park, Metodi D. Metodiev, Yonghong Shi, Benedetta Ruzzenente, Christian Kukat, Bianca Habermann; Rolf Wibom, Kjell Hultenby, Thomas Franz, Hediyе Erdjument-Bromage, Paul Tempst, B. Martin Hallberg, Claes M. Gustafsson & Nils-Göran Larsson
MTERF4 regulates translation by targeting the methyltransferase NSUN4 to the mammalian mitochondrial ribosome, Cell Metabolism, online 3 May 2011

Comprehensive study finds no link between XMRV retrovirus and chronic fatigue syndrome

Research may settle controversial findings from 2009 study

(SALT LAKE CITY)—New findings from University of Utah School of Medicine researchers show that the retrovirus called XMRV is not present in the blood of patients who have chronic fatigue syndrome (CFS). These findings contradict a widely reported 2009 Science study that linked CFS to XMRV.

The study, performed by a team of U of U researchers led by Ila R Singh, M.D., Ph.D., associate professor of pathology, was published May 4, 2011, in the Journal of Virology online, and is the most comprehensive to date regarding the purported link between chronic fatigue syndrome and XMRV.
The 2009 study linking CFS and XMRV led some CFS patients to take antiretroviral agents in hope of alleviating the symptoms of chronic fatigue syndrome, a debilitating condition of unknown cause. But in light of her new findings, Singh believes the off-label use of antiretrovirals by CFS patients is not appropriate and potentially dangerous.

"Our investigation found no trace of XMRV in any of the blood samples taken from patients we obtained ourselves, or from patients previously tested in the 2009 Science study," Singh said. "Because of our findings, we believe chronic fatigue syndrome patients should reconsider the merit of taking antiretroviral agents to alleviate their symptoms."

CFS is a devastating disorder characterized by overwhelming fatigue that is not improved by bed rest and may be exacerbated by physical or mental activity, according to the U.S. Centers for Disease Control and Prevention. It affects millions of people in the United States and worldwide. XMRV (xenotropic murine leukemia virus-related virus), which was first described in 2006, is a retrovirus. Other retroviruses are known to cause AIDS in humans, and many kinds of cancer in animals.

In 2009, a researcher at the Whittemore Peterson Institute in Reno, Nev., Judy A. Mikovits, Ph.D., published a study that found XMRV in the blood of 68 percent of CFS patients she sampled. That study, which engendered much controversy, was followed by another one performed by National Institutes of Health and the U.S. Food and Drug Administration researchers that also detected DNA sequences related to XMRV in CFS patients. Since then, however, several other studies in Europe and China found no trace of the retrovirus in CFS samples.

Singh and her colleagues in the U of U departments of anesthesiology and pathology, and ARUP Laboratories analyzed blood samples from 100 CFS patients and 200 healthy controls from the greater Salt Lake City area using molecular, serological, and viral growth assays, including assays used by researchers who previously found XMRV or XMRV-related viruses in CFS patients. CFS patients for the study were provided by the Fatigue Consultation Clinic, headed by Lucinda Bateman, M.D., in Salt Lake City.

In addition, Singh also analyzed samples from individuals from the 2009 study linking XMRV and CFS. Those samples were obtained by a third-party phlebotomy service that collected blood in home visits, de-identified the samples, and sent them to the Singh lab. Thus, the samples were not opened in any other research lab where XMRV might be present, minimizing chances of contamination. All samples were analyzed in a blinded manner.

Singh’s study is more comprehensive and differs from other studies in a number of significant ways:

- It comprises a larger set of patients who fall under well-recognized criteria for CFS
- Patients and controls were from the same geographical area, which was not true for either of the previous studies that showed a correlation between XMRV and CFS
- They analyzed blood samples using multiple, well-defined, sensitive and specific methods, including methods used in the original study
- Unlike many other studies, Singh and her colleagues used blinded methods to evaluate samples
- Singh's study tested blood samples obtained from individuals tested in the original 2009 study

XMRV is closely related to many mouse retroviruses, and contamination of blood samples or testing reagents with mouse DNA could result in a false-positive test for XMRV. Singh and her colleagues found that some of the positives obtained in other CFS-XMRV studies could be due to the presence of mouse DNA in a reagent used in testing; other positives could be attributed to carry-over of XMRV from positive controls to other samples.

In her own study, Singh initially obtained false positives for XMRV in blood samples. But she determined those false readings were related to robotic equipment that previously had been used for extraction of DNA from XMRV-infected tissue culture cells. Several months later, this equipment led to new samples getting contaminated. When the robotic equipment was abandoned, no more false positives were detected in either CFS patients or healthy patients. "It's easy to see how sample extraction and tissue culture processes might be vulnerable to contamination," Singh said.

Although she found no evidence for XMRV or any related virus in either her study samples or those tested at the Whittemore Peterson Institute, Singh says there is much data to encourage further research into whether other infectious agents are associated with CFS.

"These research efforts must continue," she says. "Chronic fatigue syndrome is a devastating disease for which a cure needs to be found."
Scientists Track Evolution and Spread of Deadly Fungus, One of the World's Major Killers

ScienceDaily (May 3, 2011) — New research has shed light on the origins of a fungal infection which is one of the major causes of death from AIDS-related illnesses. The study, published in the journal *PLoS Pathogens*, funded by the Wellcome Trust and the BBSRC, shows how the more virulent forms of *Cryptococcus neoformans* evolved and spread out of Africa and into Asia.

*Cryptococcus neoformans* is a species of often highly aggressive fungi. One particular strain of the fungus—known as *Cryptococcus neoformans* variety *grubii* (*Cng*)—causes meningitis amongst patients with compromised immune systems following HIV infection. There are believed to over up to a million cases of cryptococcal meningitis each year, resulting in over 600,000 deaths. Infection with the fungus, which invades the central nervous system, is treated with a life long therapy of antifungal drugs, which can have highly unpleasant side effects.

Sitali Simwami and Dr Matthew Fisher from Imperial College London, together with colleagues from St Georges, University of London, Naresuan University, Thailand, and the CBS Fungal Biodiversity Centre, The Netherlands, used genetic sequencing techniques to compare the genetic diversity of *Cng* in 183 samples taken from the clinic and the environment in Thailand against the 77 samples from a global database. Thailand has an emerging HIV epidemic and nearly one in five HIV-infected patients are affected by cryptococcal infection.

"Cryptococcal meningitis kills hundreds of thousands of people each year, almost as many as malaria, yet gets little attention," explains Dr Fisher. "We know very little about where it originated from and how it evolved. If we can track its evolution and diversity, then we can begin to understand where the pathogen originates from, how it infects people and how it adapts to become more—or less—virulent. This information will be valuable in helping us identify potential therapeutic targets in the future."

The researchers found that *Cng* in Thailand exhibits significantly less genetic diversity in comparison to other areas of the world, especially Africa where many different lineages of the pathogen occur. This suggests that populations of the fungus in Africa will have a wider spectrum of virulent strains and higher rates of adaptation to antifungal treatments, implying that clinicians need to pay particular attention to the risk of drug-resistant forms of the fungus here.

Their analysis also suggested that the pathogen was introduced from Africa to Asia at some point within the last 7,000 years. Many human infectious diseases are thought to have emerged within the last 11,000 years, following the rise of agriculture and domestication of animals. In particular, it supports the idea that the pathogen was imported via infected pigeons, which were domesticated around 5,000 years ago. The common pigeon, which originated in Africa, is considered to be a carrier and potential spreader of the fungus, its faeces being a common environmental source of *Cng*.

**Journal Reference:**

Revolution in Wound Care? Cotton Candy-Like Glass Fibers Appear to Speed Healing in Initial Venous Stasis Wound Trial

ScienceDaily (May 3, 2011) — Imagine a battlefield medic or emergency medical technician providing first aid with a special wad of cottony glass fibers that simultaneously slows bleeding, fights bacteria (and other sources of infection), stimulates the body's natural healing mechanisms, resists scarring, and—because it is quickly absorbed by surrounding tissue—may never have to be removed in follow-up care.

Or, imagine diabetics with hard-to-heal wounds finding a source of relief from the battle against infections and limb amputation.

Those scenarios are the hope of the developers of a revolutionary borate glass nanofiber material, which appears have sped and helped the final of healing long-term wounds in eight out of 12 venous stasis wound suffers in a recent clinical trial held at a medical center in Rolla, Mo.

Details about the trials and the glass fiber material were published in the May issue of the American Ceramic Society's *Bulletin* magazine.

The story reports on the discovery of the fibers and on an empirical study that began late in the fall of 2010 supervised by the internal review board of the Phelps County Regional Medical Center. The trial groups originally had 13 volunteer members, but one dropped out during the early stages.
According to Peggy Taylor, the PCRMC registered nurse who administered the treatments, all of the volunteers in the trial are enthusiastic about the use of the glass fiber product, which she says "looks like cotton candy."

"All of the participants had diabetes and several of them had wounds that had been unhealed for more than a year," says Taylor, a specialist in wound care. "One patient had the same wound for three years. After using the glass fiber product for a few months, we were able to repair the skin in eight of the patients. Remarkably, the other four have made a lot of progress and all of their wounds should be healed soon, too."

All of the patients suffered from problems associated with venous stasis, a condition where blood circulation in extremities is poor. As the blood pools, typically in lower legs, fluids accumulate causing unusual pressure on skin tissues. Sores and wounds can then develop when the fluid "weeps" from skin cracks, cuts or abrasions.

Because of an enzyme in the weeping fluid, the skin surrounding small venous stasis injuries can quickly erode and turn into large and deep wounds. Even small bruises can eventually develop into bone-deep openings.

The goal of the PCRMC trial was to provide an initial evaluation of the effects of the novel fibrous glass material produced by the Mo-Sci Corporation, a Rolla company already known for creating glass-based materials for medical applications.

"Bioglass" materials aren't particularly new to the medical field, but thus far all bioglass has been formed from a silica-based glass composition, and these primarily have been used in hard-tissue regeneration, such as bone repair.

Glasst scientist Steve Jung, who helped develop the new material, says he and co-developer Delbert Day had wondered whether a different type of bioactive glass material could be used for soft-tissue regeneration. "We felt from our in-vitro studies that bioactive glasses containing boron would react to body fluids much faster than silicate glasses," says Jung, who obtained his Ph.D from Missouri University of Science and Technology, where he conducted his research with Day, a professor at the university. "We also knew that an in-vitro study of lithium borate glasses had showed it to have beneficial effects against bacteria, such as E. coli, salmonella and staphylococcus microbes."

Lastly, Jung and Day recall they were interested in a composition that was rich in calcium. "Previously, investigators have reported that calcium is important for wound healing. It appears to assist the migration of epidermal cells and help the body regulate the healing process of open wounds," says Jung.

Besides composition, Jung and Day thought the structure of the material may be important to consider, too, and suspected that providing a healing "scaffold" might be beneficial. "We thought it might be advantageous to have a material that could mimic the microstructure of fibrin that forms the basis of a blood clot. We reasoned that if the structure could imitate fibrin, it might trap blood platelets and allow the formation of a wound cover that could support the healing process."

Jung and Day finally settled on a particular borate glass composition—called 13-93B3 glass—one that Mo-Sci, a company founded by Day, already knew how to form into cottony glass fibers, 300 nanometers to 5 micrometers in diameter.

After animal tests showed no adverse effects, Mo-Sci obtained a license to the material from Missouri S&T, named the borate glass material "DermaFuse," and approached PCRMC about starting the small-scale human test.

PCRMC approved the trial in July 2010, and nurse Taylor saw her first patient one month later. Once the study was underway, the company provided Taylor with individual, foil-sealed packets containing pads made of the glass fibers. She says the material is easy to apply. "It gets kind of squished in the packs, but you can form it, pick it, make it into any kind of shape you need out of it. I used tweezers to pack the material up into all of the recesses before filling the rest of the wound. I didn't pack it hard, but enough to fill all the crevices. Once it was in place, I covered it with a secondary covering or compression wrap. One thing that surprised Taylor was that the glass fibers seem to disappear over time, a phenomenon that has been observed with other bioglasses. "Does it dissolve? Does it become part of the tissue? We don't quite know, but it is just such a neat thing to watch that process."

Taylor acknowledges that under her care, the wounds would have probably healed without the glass material, but they would have required expensive vacuum-assisted healing systems that must be carried by patient at all times.
Besides low cost and ease of use, Taylor says the glass fibers seem to offer another stunning benefit: low scarring. "All but one of the patients in the trial were elderly and had a lot of skin discoloration, but we healed wounds that show nothing or negligible scarring," she says.

Jung, who now works as a senior researcher for Mo-Sci, says that the next step is expanded human trials, which will be conducted in partnership with the Center for Wound Healing and Tissue Regeneration at the University of Illinois at Chicago. He says the center has agreed to begin testing the material this summer. In the meantime, Jung says he and Day are optimistic about a new era in wound treatment. "We are really hoping the properties of these fibers can help with more extensive wounds, such as burns, and we easily foresee the day when soldiers or EMT workers carry packets of these glass fibers to provide healing protective covers that don't have to be removed."


**Eating More Salt Could Lower Chances of Heart Disease: Study**

Eating a diet high in salt may not be as bad for you as first thought and could even reduce chances of heart disease. The controversial findings question the push by authorities to get people to cut consumption.

An eight-year study by scientists in Belgium found that people who ate lots of salt were no more likely to suffer problems with heart disease or high blood pressure than people who ate less salt.

The findings ‘certainly do not support the current recommendation to lower salt intake in the general population,’ said Dr. Jan Staessen, of the University of Leuven in Belgium.

The average adult consumption is 9 g per day, 50 per cent more than is recommended.

Current UK guidelines recommend adults consume no more than 6 g of salt per day (about one teaspoon), while babies and children should have less again as their kidneys struggle with large amounts.

While previous trials suggested blood pressure readings could be improved with lower salt intake, research has yet to show whether that translates into better overall heart health in the wider population.

The researchers used data from two different studies, incorporating a total of about 3,700 Europeans who had their salt consumption measured through urine samples at the start of the studies.

Dr. Staessen and his colleagues broke the participants up into three groups: those with highest and lowest salt intakes, and those with average intake.

None of the participants had heart disease at the outset, and two thirds had normal blood pressure.

They were followed for an average of eight years, during which researchers determined how many of them were diagnosed with heart disease, and in a smaller group, how many got high blood pressure.

The findings are published in the Journal of the American Medical Association (JAMA).

The chance of getting heart and blood vessel diseases did not differ in the three groups.

However, participants with the lowest salt intake had the highest rate of death from heart disease during the follow up (4 per cent), and people who ate the most salt had the lowest (less than one per cent).

Across all three salt-intake groups, about one in four study participants who started out with normal blood pressure were diagnosed with high blood pressure during follow up.

The researchers did find that one measure of blood pressure, systolic blood pressure, increased as salt intake increased over time – but the change was very small, so it may not be important to health outcomes, said Dr. Staessen.

Reducing salt may still be a good idea for people who already have high blood pressure or who have had heart problems in the past, he added, but the study found no evidence that dietary salt causes those conditions to arise.

‘It’s clear that one should be very careful in advocating generalized reduction in sodium intake in the population at large,’ said Dr. Staessen.

‘There might be some benefits, but there might also be some adverse effects.’

The authors caution that their analysis included only white Europeans, and so the results may not translate to people of other ethnicities.

**Extended ART cost-effective for preventing mother-to-child HIV transmission in Nigeria**

Carole Leach-Lemens
Published: 05 May 2011

The World Health Organization’s (WHO) new recommendation for the extended use of triple drug antiretroviral prophylaxis for mother and infant is highly cost-effective compared to the current short-
course two drug therapy for the prevention of mother-to-child transmission (PMTCT) in Nigeria, Maunank Shah and colleagues reported in an analysis published in the advance online April edition of *AIDS*.

Scaling up the current 10% PMTCT service coverage to the existing antenatal coverage of 58% the WHO's recommendations would reduce mother-to-child transmission to 12.8% per year, compared to 16.1% with the current minimum standard of care.

7,680 cases of infant HIV and 230,400 disability-adjusted life years (DALYs) each year would be averted. (DALYs refers to the number of years of life saved in the Nigerian context, assuming that HIV infection is prevented). This represents an incremental cost-effectiveness ratio (ICER) of US$113 for each DALY averted. (Incremental cost-effectiveness ratio represents the difference in cost between using the existing intervention and the new intervention). This is highly cost-effective according to a WHO recommended willingness-to-pay threshold, which classifies any intervention that costs less than 1 x GDP per capita as highly cost-effective. (GDP per capita was US$1,191 in Nigeria in 2010).

PMTCT in Nigeria is an important public health strategy and priority. An estimated 4-12% of pregnant women are HIV-infected. Without any intervention MTCT rates are approximately 30-45%. An estimated 67,000 to 125,000 children are infected through MTCT each year. In 2009 240,000 children were reported to be living with HIV.

The current minimum standard of care comprises single-dose nevirapine (the least effective of ARV prevention strategies) or short-course combination ARV (zidovudine + lamivudine), which while more effective does not provide any benefit to the mother for her own health.

New evidence led to WHO's new recommendations for extended ART for mothers and extended prophylaxis for infants. This strategy could reduce transmission to 1-2% but is anticipated to be considerably more expensive than current strategies in Nigeria.

In light of Nigeria's plans to scale up PMTCT programmes at the national level, the authors wanted to determine whether WHO's recommendations are a cost-effective policy choice compared to the current short-course ART strategy in reducing mother-to-child transmission.

The analysis was done from a health system perspective with a target population of HIV-infected pregnant women in Nigeria and a target audience that included the Ministry of Health and public-sector health-care payers.

A decision-analysis model compared two strategies for PMTCT programme coverage:

1) The WHO new recommendation, Option B: extended maternal triple ART (zidovudine (AZT)/lamivudine (3TC)/efavirenz(EFV) starting at 14 weeks of pregnancy continued throughout breastfeeding with infant antiretroviral prophylaxis, and
2) Minimum standard of care in Nigeria: short-course ART (AZT/3TC) from the 34th week of the pregnancy to one week after delivery with single-dose nevirapine for the infant and mother during labour/delivery.

The primary outcomes were expected costs, paediatric HIV cases and total DALYs with each strategy. Incremental cost effectiveness ratios (ICERs) determined cost-effectiveness; that is the cost in US dollars for DALYs averted and the cost in US dollars for the number of HIV cases prevented when comparing the two strategies.

The authors note that from a health system perspective WHO's recommendation could potentially be cost-saving assuming the lifetime health costs for an HIV-infected child increased to more than US$17,000, or if MTCT rates were to exceed 20%.

Estimated costs if coverage were extended to current pregnancy rates using the WHO recommendation or the minimum standard of care would be US$48 million a year, and $10.5 million a year, respectively. While considerable funding is received from PEPFAR and the Global Fund for HIV/AIDS services, a 2010 audit showed US$5.8 million was spent on PMTCT services.

The average health system cost for each pregnancy using the WHO recommendation and the MSOC would be US$401 and US$293, respectively.

The authors note maintaining coverage at the current level of 10% using the MSOC would cost the Nigerian health system approximately US$93,000,000 a year resulting in the most expensive and least cost-effective choice. Offering the WHO recommendation at 100% coverage would cost the same.

The study authors noted a number of limitations, including difficulties in estimating lifetime treatment costs for an HIV-infected child, the lack of inclusion of any health care costs averted as a result of maternal treatment, and an assumption that uptake of voluntary counselling and testing, as well as PMTCT interventions, would be high among Nigerian women.
However they say that their model can help guide scale-up plans by demonstrating the potential cost-effectiveness of different levels of coverage, allowing informed decision-making about how to allocate scarce resources.

The authors note cost-effectiveness is dependent upon the lifetime costs of caring for infants infected perinatally and the efficacy of ARV regimens and add “Despite potential variability in these parameters sensitivity analysis suggests an almost 100% chance that the WHO recommendation...is the preferred [and most cost-effective] option for PMTCT.”

Reference

New Contraceptive in the Pipeline
Australian Associated Press, (05.04.2011) Nicky Park
Scientists at the University of Newcastle in New South Wales are developing a gel-based contraceptive that also will protect against STDs.

Speaking at the Australian Academy of Science’s Shine Dome in Canberra this week, John Aitken, a reproductive researcher and professor at the university, said the gel could be applied to a small, pliable sponge inserted into the vagina up to 48 hours before sexual intercourse. When semen makes contact with the gel, the sperm are paralyzed and any STD-causing organisms are killed. The contraceptive would be marketed to females ages 15-25. “[They] are the ones who are more susceptible to sexually transmitted disease and unwanted pregnancies,” he said. The gel has yet to undergo animal and human trials.

Aitken noted that currently there are no “local compounds” that can be used as an STD preventive. Pregnancy-inhibiting spermicides are “crude,” he said. “Women who use a lot of this stuff, especially commercial sex workers, are significantly more likely to get HIV than women who don’t use it ... it just destroys everything around it,” he added. “You want to be able to have intercourse in the safe knowledge you will neither get pregnant, nor will you catch some terrible microbe.”

According to Aitken, there have been no groundbreaking developments in contraception since the birth control pill was introduced. “We need contraceptives that meet the demands of the 21st century and one of those demands is that there’s now a much higher risk of contracting an [STD] than there was in the 1950s and ’60s,” he said. “Globally there is a pandemic in sexually transmitted disease so we need to develop new forms of contraception that take that into account.”

'Confluence Of Circumstances' Resulted In Haitian Cholera Outbreak, U.N.-Appointed Panel Says
Haiti’s cholera outbreak, which started last October, “was caused by a South Asian strain that contaminated a river where tens of thousands of people wash, bath, drink and play,” a report (.pdf) from an independent U.N.-appointed panel said on Wednesday, the Associated Press reports. “Although many have blamed the epidemic on U.N. peacekeepers from South Asia working in Haiti, the report issued by the panel declined to point the finger at any single group for the outbreak, saying it was the result of a 'confluence of circumstances’” (5/4).

Evidence "overwhelmingly supports' the conclusion that" human activity contaminated a "tributary of the Artibonite River with a pathogenic strain of cholera“ and resulted in the epidemic, the report says, the U.N. News Centre writes. "The introduction of this cholera strain as a result of environmental contamination with faeces could not have been the source of such an outbreak without simultaneous water and sanitation and health-care system deficiencies," according to the findings of the report. "These deficiencies, coupled with conducive environmental and epidemiological conditions, allowed the spread of the Vibrio cholerae organism in the environment, from which a large number of people became infected," the report notes, concluding that the outbreak "was not the fault of, or deliberate action of, a group or individual” (5/4).

"Panel members said Haiti’s outbreak underscored the need for U.N. personnel and other first responders coming from countries where cholera is endemic to be screened for the disease, receive a prophylactic dose of appropriate antibiotics before departure, or both,” the AP reports. The report also called for the U.N. to install on-site fecal waste systems in its locations around the world (5/4).

U.N. Secretary-General Ban Ki-moon said he planned to “convene a task force” to examine the report recommendations, the Wall Street Journal reports (Lauria, 5/5).
Medical Group Detects Rise In Rural Cholera Cases In Haiti
In related news, Partners in Health said on Wednesday that it has detected an increase in cholera cases in rural areas of Haiti and is worried the outbreak might begin to surge with the start of the spring rainy season, the AP/Seattle Times reports. "At centers in Mirebalais, a central town near where the outbreak was first detected in October, the number of new cholera patients has roughly tripled in recent weeks, [PIH spokesperson Kathryn] Mahoney said," the news service writes.

"However, Doctors Without Borders, which has had a leading role in responding to the cholera outbreak, is more optimistic. The group's workers have seen a slight increase in new cases in the countryside but the overall number of cases in the country has been stable, said Sylvain Groulx, the group's chief of mission in Haiti," the AP reports. "These are little, little spikes," Groulx said. "We're not expecting to see a second peak" (5/4).

Researchers propose 'whole-system redesign' of US agriculture
Transformative changes in markets, policy and science, rather than just incremental changes in farming practices and technology, will be critical if the United States is to achieve long-term sustainability in agriculture, according to a nationwide team of agriculturists that includes a University of California, Davis, animal scientist.

The team's recommendations, first published as a 2010 report by the U.S. National Research Council, appear as a Policy Forum piece in the May 6 issue of the journal Science. Lead author on the paper is John Reganold, Regents Professor of soil science and agroecology at Washington State University, Pullman.

"For decades, the agricultural industry, research community and government, have looked to incremental improvements in agricultural procedures and technologies for achieving advances in productivity," said Deanne Meyer, a Cooperative Extension livestock waste management specialist in the UC Davis Department of Animal Science and a member of the research team.

She noted that such incremental improvements have included adoption of two-year crop rotations, precision agriculture technologies, classically bred and genetically engineered crops, and reduced- or no-tillage management systems.

"While all of these have resulted in important improvements, it's become apparent that as modern agriculture also grapples with important issues such as global climate change, biodiversity, resource conservation and public health problems, a more transformative approach is needed," she said.

Such an approach would balance production goals with long-term sustainability concerns involving the environmental, social and economic impacts of agriculture. It would focus on a "whole-system redesign" that would address policy and market issues, as well as technological issues, the researchers recommend in their report.

The approach would incorporate innovative agricultural systems such as organic farming, grass-fed and other alternative livestock production systems, mixed crop and livestock systems, and perennial grains. And it would require significant changes in market structures, policy incentives and public funding for agricultural science, according to the report.

The research team suggests that with a new version of the U.S. Farm Bill due in 2012, the time is now ripe to begin reforming U.S. agriculture.


Hunting for Deadly Bacteria
ScienceDaily (Apr. 12, 2011) — You can't see them, or smell them or taste them. They can be in our water and in our food, multiplying so rapidly that conventional testing methods for detecting pathogens such as E.coli, Salmonella and Listeria come too late for the tens of thousands of Canadians who suffer the ill effects of these deadly bacteria.

Biochemist Yingfu Li and his research team have developed a simple test that can swiftly and accurately identify specific pathogens using a system that will 'hunt' for bacteria, identifying their harmful presence before they have a chance to contaminate our food and water.

Like any living thing, bacteria have their own spoor, leaving behind DNA trails of bacterial 'droppings'. Li tracks these metabolic by-products with molecular beacons—little lighthouses on a molecular scale that actually light up when they detect the DNA sequence left behind.

Li created a DNAzyme sensor that will be able to identify any bacteria, utilizing a method that doesn't require the steps and specialized equipment typically used to identify whether or not harmful bacteria are present.
"Current methods of foodborne bacterial detection take time. The five days it takes to detect listeria, for example, can translate into an outbreak that costs lives. We have developed a universal test that uses less complex procedures but still generates precise and accurate results," says Li, a Canada Research Chair in Directed Evolution of Nucleic Acids.

Li's fluorescent test system was highlighted in Angewandte Chemie International Edition. Li's paper, co-authored with lab members Monsur Ali, Sergio Aguirre and Hadeer Lazim, was designated a 'hot paper' by Angewandte's editors for its "importance in a rapidly evolving field of current interest."

"McMaster researchers are known for their ability to provide solutions to problems that impact the public's well-being. The test that Professor Li has developed will help safeguard the health of Canadians, and supply industry with a reliable means to bring safe food products to consumers and reduce their time to market," said Mo Elbestawi, vice-president, research and international affairs.

Journal Reference:

Protein Discovered That Could Help Prevent the Spread of Cancer
ScienceDaily (May 5, 2011) — A protein capable of halting the spread of breast cancer cells could lead to a therapy for preventing or limiting the spread of the disease.

"Cancer researchers want to design new therapeutic strategies in which the metastasis or spreading stage of cancer can be blocked," explains Andrew Craig, lead researcher and a professor in Queen's Department of Biochemistry and Cancer Research Institute. "Patients stand a much better chance of survival if the primary tumor is the only tumor that needs to be treated."

The regulatory protein identified by Dr Craig's team inhibits the spread of cancer cells by removing and breaking down an invasive enzyme on the surface of cancer cells. If it remains unchecked, this enzyme degrades and modifies surrounding tissues, facilitating the spread of cancer through the body.

Dr. Craig hopes that his team's findings may help develop more targeted therapies that have a specific inhibitory function on this enzyme that is implicated in certain metastatic cancers.

Traditional therapies that have been used to counteract the invasive nature of this particular enzyme also destroy other enzymes that are important for the body's normal physiological function.

The researchers examined a network of proteins that are responsible for controlling the shape of cancer cells. They focused specifically on parts of the cell that protrude into surrounding body tissues, allowing the cancer cell to degrade surrounding tissue barriers.

Normal cells also produce similar protrusions as part of a healthy physiological process that allows cells to move through body tissues during an immune response.

During the spread of cancer these normally healthy mechanisms are coopted by cancer cells, allowing the cancer to break through tissue boundaries and colonize distant tissues. This process of cancer spread is known as metastasis and is frequently the cause of cancer-related deaths.

Journal Reference:

Worm Discovery Could Help One Billion People Worldwide
ScienceDaily (May 5, 2011) — Scientists have discovered why some people may be protected from harmful parasitic worms naturally while others cannot in what could lead to new therapies for up to one billion people worldwide.

Parasitic worms are a major cause of mortality and morbidity affecting up to a billion people, particularly in the Third World, as well as domestic pets and livestock across the globe.

Now, University of Manchester researchers have, for the first time, identified a key component of mucus found in the guts of humans and animals that is toxic to worms.

"a thick layer of mucus," explained Dr David Thornton, from the University's Wellcome Trust Centre for Cell Matrix Research. "The mucus barrier is not just slime, but a
complex mixture of salts, water and large 'sugar-coated' proteins called mucins that give mucus its gel-like properties.

"In order to be able to study these debilitating worm diseases, we have been using a mouse model in which we try to cure mice of the whipworm Trichuris muris. This worm is closely related to the human equivalent, Trichuris trichiura.

"We previously found that mice that were able to expel this whipworm from the gut made more mucus. Importantly, the mucus from these mice contained the mucin, Muc5ac. This mucin is rarely present in the gut, but when it is, it alters the physical properties of the mucus gel."

Co-lead on the study, Professor Richard Grencis, from the Faculty of Life Sciences, continued: "For this new research, we asked how important Muc5ac is during worm infection by using mice lacking the gene for Muc5ac. We found that mice genetically incapable of producing Muc5ac were unable to expel the worms, despite having a strong immune response against these parasites. This resulted in long-term infections.

"Furthermore, we discovered the reason for the importance of Muc5ac is that it is 'toxic' for the worms and damages their health."

The study, published in the Journal of Experimental Medicine and featured in Nature’s ‘research highlights’ today (Thursday), found that Muc5ac is also essential for the efficient expulsion from the gut of other types of worm that cause problems in humans. These include the hookworm, and the spiral threadworm. Together, these worms cause mortality and morbidity in up to one billion people across the globe.

Dr Sumaira Hasnain, the lead experimentalist on the project, added: "For the first time, we have discovered that a single component of the mucus barrier, the Muc5ac mucin, is essential for worm expulsion. Our research may help to identify who is and who isn’t susceptible to parasitic worms, and it may eventually lead to new treatments for people with chronic worm infections."

Journal Reference:

Hundreds of girls raped, murdered in Tanzania for black magic AIDS ‘cure’
By Reuters
Thursday, May 5th, 2011—11:18 am
Share 3 20 28 Share 1 Share 2
DAR ES SALAAM (Reuters) – Hundreds of albinos are thought to have been killed for black magic purposes in Tanzania and albino girls are being raped because of a belief they offer a cure for AIDS, a Canadian rights group said on Thursday.

At least 63 albinos, including children, are known to have been killed, mostly in the remote northwest of the country.

"We believe there are hundreds and hundreds of killings in Tanzania, but only a small number are being reported to the police," Peter Ash, founder and director of Under The Same Sun (UTSS), told Reuters.

"There is belief that if you have relations with a girl with albinism, you will cure AIDS. So there are many girls with albinism who are being raped in this country because of this belief, which is a false belief."

Around 1.4 million Tanzanians among a population of 40.7 million have the HIV virus that leads to AIDS.

Albino hunters kill their victims and harvest their blood, hair, genitals and other body parts for potions that witchdoctors say bring luck in love, life and business.

"(It is believed) a person with albinism is a curse. They are from the devil, they are not human, they do not die, they simply disappear," said Ash.

Ernest Kimaya, head of the Tanzania Albino society and a sufferer of the pigment disorder, said social stigma prevented many girls from reporting rape, making it difficult to say how many albinos had been sexually abused.

"These things are taking place underground. Even the albino killings started quietly, before the atrocities were finally exposed in public," Kimaya told Reuters.

Activists last week reported three murders of teenage albino boys from the same family in northern Tanzania, who were poisoned and their bones later robbed from their graves.
The Tanzanian government says it is determined to halt the macabre killings, but has been widely criticized for inaction.

**Albinos in Tanzania murdered or raped as AIDS "cure"**

Fumbuka Ng’wanakilala

Reuters US Online Report Health News

May 05, 2011 04:57 EDT

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By H. Steven Wiley

**If Bacteria Can Do It...**

**Learning community skills from microbes**

Andrzej Krauze

One of the greatest joys of being a scientist is continuously having the opportunity to see the world in new ways. At a national laboratory or research university, you’re exposed to many different fields of research, from which you can always glean something useful. My current fascination is learning about microbial communities and how they thrive by achieving just the right balance between cooperation and competition.

My training is in biochemistry and cell biology, but I was exposed to medical microbiology during a stint as a faculty member in a medical school. There my view of microbes was tainted by the perspective of my colleagues, who saw them either as pathogens or as opportunistic organisms that contaminated tissue-culture plates. My view of cell communities, conversely, came from my research in cancer biology, where I saw the cooperative cell assemblies of normal tissues as driven by genetic programming. Without this enforced cooperation, cells would become selfish, dooming the organism to death by cancer.

This was a simplistic view, based on the idea that natural selection only operates at the level of the individual. A more nuanced appreciation of evolutionary theory reveals that a behavior such as altruism can benefit genetic lineages even when it does so at the expense of the individual. Still, my bias remained that cooperation was something genetically encoded. Then I learned about microbial communities and what they can teach us about thriving within constraints.

Numerically and by biomass, bacteria are the most successful organisms on Earth. Much of this success is due to their small size and relative simplicity, which allows for fast reproduction and correspondingly rapid evolution. But the price of small size and rapid growth is having a small genome, which constrains the diversity of metabolic functions that a single microbe can have. Thus, bacteria tend
to be specialized for using just a few substrates. So how can simple bacteria thrive in a complex environment? By cooperating—a cooperation driven by need.

Bacteria rarely live in a given ecological niche by themselves. Instead, they exist in communities in which one bacterial species generates as waste the substrates another species needs to survive. Their waste products are used, in turn, by other bacterial species in a complex food chain. Survival requires balancing the needs of the individual with the well-being of the group, both within and across species. How this balancing act is orchestrated can be fascinating to explore as the relative roles of cooperation, opportunism, parasitism and competition change with alterations in available resources.

The dynamics of microbial behavior are not just a great demonstration of how the laws of natural selection work and how they depend on the nature of both selective pressures and environmental constraints. Microbial communities also demonstrate important nongenetic principles of cooperation. And herein lie lessons that scientists can emulate.

To be successful, scientists must be able to compete not only for funding, but for important research topics that will give them visibility and attract good students. In the earlier days of biology, questions were more general, making it easier to keep up with broad fields and to exploit novel research findings as they arose. As the nature of our work has become more complex and the amount of biological information has exploded, we have necessarily become more specialized. There is only so much information each of us can handle.

specialization has come an increasing dependence on other specialized biologists to provide us with needed data and to support our submitted papers and grants. At the same time, resources have become scarcer, and we find ourselves competing with the same scientists on whom we are becoming dependent. Thus, it is necessary to find a balance between cooperation and competition in order to survive, and perhaps even to thrive.

The composition of microbial communities is driven by both the interaction of different species and external environmental factors that determine resource availability. Scientists want to learn the rules governing these complex relationships so they can reengineer bacterial communities for the production of useful substances, or for bioremediation. Perhaps as we learn the optimal strategies that microbial communities use to work together effectively, we will gain insights into how we can better work together as a community of scientists.

H. Steven Wiley is lead biologist for the Environmental Molecular Sciences Laboratory at Pacific Northwest National Laboratory.

Abacavir linked to heart disease, stroke, tenofovir to heart failure, in large US study

Keith Alcorn
Published: 06 May 2011

A large study of US patients with HIV has concluded that people taking abacavir had an increased risk of heart disease and stroke, but also found a modestly increased risk of heart failure in people taking tenofovir.

The study, which analysed patient data from the Veterans Administration Clinical Case Registry, was published this month in the journal AIDS.

There has been controversy for some years over the possible role of abacavir in cardiovascular disease in people with HIV, since the D:A:D cohort study found that recent abacavir treatment increased the risk of heart attack by 90%.

While some cohort studies have found that people who took abacavir as part of their antiretroviral regimen had a higher risk of heart attack, other studies—including a meta-analysis of clinical trials of the drug—found no increased risk of cardiovascular events in people taking the drug.

Less attention has been paid to heart failure, a progressive condition caused by weakening of the heart, attributable both to the same risk factors as heart attack and atherosclerosis, but also to the toxicity of HIV or drugs to the heart muscles.

The study published this month analyses cardiovascular events in 10,931 HIV-infected patients receiving care through Veterans Health Administration hospitals in the United States who started antiretroviral therapy between 1997 and 2007, and who had viral load, CD4 count and kidney function data available.

The kidney function data were important, authors noted, because most previous studies have not controlled for an important potential bias: patients with kidney disease may be steered away from tenofovir due to its potential toxic effect to the kidney tubules, and placed instead on abacavir-based
treatment. However people with kidney disease are at higher risk of cardiovascular disease, and this could lead to an apparent increase in the risk of cardiovascular events that might not be caused by abacavir.


This analysis compared treatment outcomes in 3,235 patients treated with abacavir, 4,314 treated with tenofovir and 9,122 who received regimens containing other antiretroviral drugs.

The average duration of exposure to abacavir was 1.6 years and to tenofovir 1.3 years.

Conditions strongly implicated in the development of cardiovascular disease were common in this cohort: around half smoked, around 40% had high blood pressure, 16-19% had diabetes and one-fifth already had a diagnosis of cardiovascular disease at the time they started either abacavir or tenofovir.

Impaired kidney function was somewhat more common in the abacavir-treated patients compared to tenofovir-treated patients (10% vs 6%).

During 60,588 person-years of follow-up there were 194 cases of heart failure, while in 59,578 person-years of follow-up there were 501 atherosclerotic cardiovascular events.

Abacavir treatment was associated with a 50% increase in the risk of a cardiovascular event when compared to tenofovir or other treatment (13.4 events vs 9.4 events per 100 person years, p<0.01; hazard ratio 1.49 (95% confidence interval 1.09–2.05)), even after controlling for measures of kidney function and changes in kidney function over time.

When different types of cardiovascular event were isolated, abacavir treatment was significantly associated with stroke (2.05, 95% CI 1.00–4.19) but not with other cardiovascular events and duration of exposure or less recent exposure to abacavir were not associated with an increased risk of a cardiovascular event.

Tenofovir treatment was associated with an 82% increase in the risk of heart failure in multivariate analysis (HR = 1.82, 95% CI 1.02 – 3.24, p=0.04) when compared to use of abacavir or other drugs, and the authors report that this association appeared stronger in patients with poorer kidney function (GFR <60 mL/min/1.73m² (HR = 3.29, 95% CI 1.39 – 7.76).

Besides the known effect of tenofovir on kidney function, which tends not to be profound in observational studies, the authors ask whether another mechanism might be at work.

They note that tenofovir can cause damage to the lining of the kidney tubules, and so may disrupt both vitamin D activation and correct balance of calcium and phosphate. Renal mineral bone disease, characterised by abnormal metabolism of vitamin D, calcium and phosphate, has been associated with cardiovascular disease, and the authors say that there is an urgent need to determine whether tenofovir treatment might lead to a higher rate of heart failure through this pathway.

The authors caution that their results may not be generalisable to women, who comprised less than 3% of the cohort receiving abacavir or tenofovir.

Reference

Antibodies Help Protect Monkeys From HIV-Like Virus: Finding Could Aid Development Of HIV Vaccine For Humans
06 May 2011

Using a monkey model of AIDS, scientists have identified a vaccine-generated immune-system response that correlates with protection against infection by the monkey version of HIV, called simian immunodeficiency virus (SIV). The researchers found that neutralizing antibodies generated by immunization were associated with protection against SIV infection. This finding marks an important step toward understanding how an effective HIV vaccine could work, according to scientists who led the study at the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health.

Scientists administered the SIV vaccine to half of the 129 monkeys in this study and a placebo vaccine to the other half. The scientists then gave each monkey up to 12 doses of one of two forms of SIV through rectal injection to simulate sexual exposure to the virus. The vaccine regimen did not protect the monkeys that received one form of SIV, but it reduced the rate of infection by 50 percent in the monkeys that received the other form of the virus.

To learn how the vaccine worked, the study team examined a variety of immune responses and certain genetic factors in the monkeys that the vaccine protected. The scientists found that SIV neutralizing
antibodies and the activation of white blood cells known as helper CD4+ T cells correlated with the protective effect. Also, monkeys that expressed two copies of a gene known to help limit SIV replication were better protected by the vaccine than monkeys that did not, demonstrating that genetic factors can contribute to protection.

This study provides evidence that neutralizing antibodies are an important part of the immune response needed to prevent HIV infection. The ability of the vaccine regimen to protect monkeys from SIV infection is comparable to the results seen in the RV144 trial with 16,000 adult volunteers in Thailand; RV144 was the first HIV vaccine study to demonstrate a modest protective effect, reducing the rate of HIV infection by 31 percent. The new research also provides an animal model to better understand the immune basis for vaccine protection against lentiviruses, a subclass of viruses that includes HIV and SIV. This knowledge will help guide strategies for the future development of AIDS vaccines.

The SIV vaccine regimen used in this study was similar to an HIV vaccine regimen currently being tested in humans in the NIAID-funded clinical trial known as HVTN 505. Both vaccine regimens consist of priming with a vaccine made from DNA that encodes immunodeficiency virus proteins, followed by boosting with an inactivated cold virus (adenovirus) that contains immunodeficiency virus proteins.


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**Injection Drug Use Helps Drive HIV/AIDS in Africa**

*Voice of America News*, (04.29.2011) Joe DeCapua

In many countries experiencing a stabilizing of HIV incidence, the proportion of injection drug use (IDU)-related infections is increasing, say researchers with the Center for Strategic and International Studies (CSIS) in Washington.

The problem is evident in sub-Saharan Africa, where heroin routes have expanded. The uptick in African IDU-related infections is traceable to the late 1990s, when “white” heroin became available in East Africa.

“I think the whole question of [IDU] and HIV prevention has been one that’s really under-resourced and not really paid adequate attention to, either from a policy or a programmatic point of view,” said Lisa Carty, co-author of a CSIS report on the problem.

Epidemiological data of the type needed for planning and effective treatment and prevention programs remain patchy, says the CSIS report.

Coastal areas such as Mombasa, Zanzibar, and Dar es Salaam “have become more and more an entry point for drug trafficking out of the South Asia region, in through Africa and then, very often, up through Europe and on to the United States,” Carty said.

Women are especially at risk, since “many women who inject drugs turn to sex as a way of raising money to buy drugs,” said report co-author Dr. Phil Nieberg, senior associate with Global Health Policy Center. “So there’s an overlap between sex work and drug use.” Ironically, even male IDUs disparage female drug injectors, he said.

Treating addiction as a disease rather than a crime could encourage more addicts to seek help, Nieberg and Carty said. Counseling, needle-exchange programs, and methadone maintenance treatment could be a part of that, they said. Law enforcement efforts tend to push IDUs further away from care and treatments, a situation that affects sex workers as well as men who have sex with men.

**New NRTI Microbicide Looks Promising in Lab**

**SUMMARY**

A novel vaginal microbicide gel containing the reverse transcriptase inhibitor IQP-0528 demonstrated good antiviral activity and safety in laboratory studies.

*By Liz Highleyman*

Researchers are working on several biomedical HIV prevention strategies, ranging from vaccines to pre-exposure prophylaxis (PrEP). Microbicides containing antiretroviral drugs have received considerable attention, especially given the promising results from the CAPRISA trial testing a tenofovir-based gel in women in South Africa.

As described in the *April 2011 issue of Antimicrobial Agents and Chemotherapy*, Alamulu Mahalingam from the University of Utah and colleagues evaluated the safety and antiviral efficacy of a pyrimidinedione compound known as IQP-0528 being developed by ImQuest BioSciences. This agent was
selected for further development due to its stability under physiologically relevant conditions, a wide therapeutic window, and antiviral activity in the nanomolar range.

The researchers developed 2 vaginal gels formulations containing IQP-0528, one using 3.0% hydroxyethyl cellulose, the other 0.65% Carbopol polymer. The properties of these gels were evaluated in laboratory studies using cells lines and human cervical tissue samples.

**Results**

- The gels demonstrated physical and chemical stability for 3 months.
- The 3.0% HEC gel had the best potential bioavailability and was selected for safety and activity evaluations.
- In vitro and ex vivo safety evaluations of 3.0% HEC gel containing 0.25% IQP-0528 showed "no significant loss in cell viability or significant inflammatory response."
- An in vitro HIV-1 entry inhibition assay showed that this formulation had a 50% effective concentration of 0.14 mcg/mL in culture media.
- In ex vivo cervical tissue, the gel demonstrated "complete protection against HIV infection."

Based on these findings, the researchers concluded, "these results are encouraging and warrant further evaluation of IQP-0528 gel formulations in vivo models, as well as the development of alternative formulations for the delivery of IQP-0528 as a microbicide."

"[T]his formulation is expected to provide complete protection against infection with no significant toxicity or irritation to vaginal tissue," they added in their discussion. They estimated that the cost of the gel could be as low as 30 cents per dose, making it affordable in resource-limited settings.

**Malaria Mosquitoes Accurately Find Their Way to Smelly Feet**

ScienceDaily (May 6, 2011) — Malaria mosquitoes utilize CO$_2$ from exhaled air to localize humans from afar. In the vicinity of their preferred host, they alter their course towards the human feet. Researcher Remco Suer discovered how female malaria mosquitoes use foot odors in the last meters to guide them to their favoured biting place. Suer, who is defending his doctoral thesis May 9 at Wageningen University, part of Wageningen UR, sees possibilities to disrupt the host seeking behaviour of the malaria mosquito.

African malaria mosquitoes, *Anopheles gambiae*, use their olfactory organs, two antennae, two mouthparts (maxillary palps) and the proboscis, to search for their hosts to obtain a bloodmeal. From a distance of several tens of meters mosquitoes detect CO$_2$ which forms part of exhaled air by humans. However, a malaria mosquito does not follow the CO$_2$ trail to its source, the mouth, but at a certain point close to the source is diverted toward the feet, which is the preferred biting place for this mosquito species.

PhD candidate Remco Suer from the chair group Entomology of Wageningen University has uncovered a mechanism for this behavior. Previous research within this project, funded by the Bill and Melinda Gates foundation, showed that bacteria living on the human foot produce various odors and identified ten bacterial foot odors that, when offered as a blend, were attractive to malaria mosquitoes. Remco Suer now shows that nine out of these ten foot odors are detected by olfactory neurons present underneath hair-like structures on the mouthparts of the malaria mosquito. More importantly, he discovered that 5 of the 10 microbial odors are capable of blocking the response to CO$_2$. By blocking the CO$_2$ signal the mosquito stops orienting towards CO$_2$ and diverts its attention to close range foot odors.

The researcher added additional CO$_2$ to the experiments to simulate exhaled air. A short stimulation of 1 second with the highest concentration of the five foot odors separately resulted in complete inhibition of the CO$_2$ response for multiple seconds.

From dozens of olfactory neurons, only one type of olfactory neuron is capable detecting CO$_2$. This olfactory neuron is co-compartmentalized together with two other olfactory neurons underneath the capitate peg sensilla, hair-like structures, present on the mouthparts of the mosquito. By registering the responses of these olfactory neurons, Suer was able to determine which human odors the female malaria mosquito detects. From the ten microbial odors previously discovered nine elicited responses from all three olfactory receptors on the mouthparts and 5 of them inhibited the CO$_2$ response.
By inhibiting the perception of CO₂, it is possible to disrupt the host seeking behavior of the malaria mosquito. Because these bacterial foot odors block the CO₂ response and at the same time activate other olfactory neurons, it is very plausible that these odors cause the switch from the long distance CO₂ signal to the preferred biting place, the feet. Behavioral experiments show that at short range these odors block the CO₂ effect and even enhance the attractiveness of an attractive basic odor blend. This implies that these CO₂ inhibitors cannot be used as repellents and even divert the orientation of the mosquito to short-range human odors.

Odors that block the CO₂ receptor but activate other olfactory neurons, thereby diverting the orientation of the malaria mosquito to other odor sources, have potential applications in odor trapping systems as a barrier. By placing a barrier releasing these CO₂ inhibitors, it might be possible to lure malaria mosquitoes towards odor traps containing a mixture of other attractive human odors.

Anatomy of an Outbreak: Tiny Changes in Chikungunya Virus Separate Epidemic African Strain and Tamer Asian Variety

ScienceDaily (May 5, 2011) — What causes a virus to suddenly begin infecting large numbers of people? Scientists have long known that the process they call "viral emergence" involves a wide variety of factors. Some are changes in the environment, either generated by natural causes or human activity. Others are internal, arising from accidental changes—mutations—in the virus' genetic code.

Studying such mutations in different strains of the chikungunya virus has helped University of Texas Medical Branch researchers solve one of the most puzzling mysteries of chikungunya's emergence in Asia. They describe their results in an article in the Proceedings of the National Academy of Sciences.

Chikungunya, which originated in Africa, is carried by mosquitoes and causes intensely painful arthritis that can last for months or years. Thanks to a discovery made at UTMB, scientists know that the virus' rapid spread was launched by a single mutation in an African strain of the virus.

The alteration was so small—a single amino acid change in one of the virus' exterior "envelope" proteins—that a researcher compared it to "a single missing comma in a six-page short story." But this so-called "E1-A226V mutation" made it possible for the virus to efficiently infect Aedes albopictus, a species of mosquito found nearly worldwide.

The mutated strain of the virus took full advantage of its new host, infecting millions of people as it spread across India, Thailand and Malaysia. It even jumped to northern Italy, carried by an infected traveler, where it established itself in the local Aedes albopictus mosquito population.

This albopictus-adapted strain's success raised a fundamental question, for this was not chikungunya's first visit to Asia. Strains of the virus transmitted by another mosquito species, Aedes aegypti, have caused sporadic outbreaks there for nearly six decades. If the virus was changing all the time, and only one minor mutation was necessary to switch the virus from aegypti to albopictus—a more widespread vector—why hadn't that mutation happened in the strains that had arrived in Asia 60 years before?

"Asia is Aedes albopictus' native territory, but we can't find any evidence of chikungunya transmission by albopictus until the arrival of this new strain," said UTMB pathology professor Scott Weaver, senior author on the PNAS paper. "It was surprising to us that strains of this apparently very adaptable virus circulated in Asia for 60 years without making the adaptation that would allow them to be transmitted by albopictus."

To find out what was going on, Weaver and his colleagues—lead author and postdoctoral fellow Konstantin Tsetsarkin, postdoctoral fellow Rubing Chen, research technician Grace Leal, assistant professor Naomi Forrester, professor Stephen Higgs, and research associate Jing Huang—conducted experiments based on the hypothesis that some part of the Asian chikungunya strains' genetic code was suppressing the key mutation whenever it occurred and thus keeping it from infecting Aedes albopictus.

Using two different Asian strains into which they inserted the E1-A226V mutation, they systematically added additional genetic portions from the African strain, followed by specific mutations to determine which interacted with E1-A226V. Then they tested each change to see whether it affected Aedes albopictus infectivity.

Ultimately, they found that a single genetic element—which also changed an amino acid in the same envelope protein altered by the E1-A226V mutation—increased the Asian chikungunya strains' ability to infect Aedes albopictus by a hundredfold.

"This old Asian lineage needs an additional mutation to adapt to Aedes albopictus, and we think that's what protected India and Southeast Asia from much larger epidemics over the last 60 years," Weaver said.
"But some African strains only needed one mutation to spark much larger outbreaks. And now, a strain that emerged from Africa in 2004 seems to be displacing the old Asian strains wherever it goes."

The chikungunya story, Weaver said, demonstrates how small genetic differences among viruses can have dramatic and unexpected effects on their ability to cause human disease. This study also will allow researchers to predict the amount of disease chikungunya may cause if it becomes endemic in the Americas.

"We don't really have the ability to predict when these viruses are going to suddenly mutate and change from one host to another. We can figure out how it happened retrospectively, but we have no idea how many near misses there are," Weaver said. "This was an opportunity to understand one situation where for a long time epidemic emergence didn't happen for a virus in Asia, and how it did happen suddenly when another strain got loose from Africa and started spreading around the globe."

Journal Reference:

DNA from Common Stomach Bacteria Minimizes Effects of Colitis, Study Says

ScienceDaily (May 6, 2011) — DNA from Helicobacter pylori, a common stomach bacteria, minimizes the effects of colitis in mice, according to a new study by University of Michigan Medical School scientists.

The study published in Gut this month was performed by a team of investigators assembled by senior author John Y. Kao, M.D. of the University of Michigan’s Division of Gastroenterology and assistant professor in U-M’s Department of Internal Medicine. The findings indicate that DNA from H. pylori significantly ameliorates the severity of colitis, say lead authors Jay Luther, M.D. and Stephanie Owyang, an undergraduate student on the team.

Colitis involves inflammation and swelling of the large intestine that leads to diarrhea and abdominal pain. Approximately 3.3 million people in the U.S. suffer from colitis.

More than half of the people in the world are infected with H. pylori, although only about 20 percent of U.S. residents have it. In the U.S., H. pylori infection is treated in patients with stomach ulcers or cancers with antibiotics, but the majority of infected individuals don’t notice they have it and may not develop ulcers or cancers. "This research shows further evidence that we should leave the bugs alone because there may be a benefit to hosting them in the stomach," says Kao.

"H. pylori has co-existed with the human race for more than 50,000 years and although it is linked with peptic ulcer disease and stomach cancer, only a minority of infected patients will develop those complications," says Luther, adding that less than 15 percent of H. pylori-infected patients develop peptic ulcer disease and less than 1 percent develop cancer.

The researchers aren’t advocating infecting people with H. pylori to treat colitis, but say this may indicated that those already carrying the bacteria should not be treated unless they develop symptoms. These findings also raise significant concerns about global vaccination against H. pylori.

"This bug could be good for you, and we need to understand better what it does," says Owyang.

The H. pylori infection is more commonly found in developing countries or those with poor sanitation, where colitis, Salmonella and inflammatory bowel diseases are less common. Most people contract H. pylori in their first seven years of life, most commonly through an oral-fecal route.

In the study, researchers found that H. pylori DNA is uniquely immunosuppressive containing high numbers of sequences known to inhibit inflammation. They isolated the DNA from both H. pylori and another bacterium, E. coli, for further comparison. They found that mice receiving H. pylori DNA displayed less weight loss, less bleeding and greater stool consistency compared with mice infected with E coli DNA.

"With one dose, there was a significant difference in the bleeding and inflammation in the colon," says Luther. "However, further study is needed to define other potential protective measures that H. pylori may provide and its safety as a treatment in patients."

In previous research, U-M gastroenterologists also found that H. pylori reduced the severity of inflammation of the colon caused by Salmonella in mice.

"It is amazing that the bacterial DNA not only directs the biological behavior of the bacteria, but also has a significant influence on gut immunity of the host. This information might have important implications down the line in our understanding of disease manifestation," says Owyang.

Journal Reference:
**Studies solve mystery of 'HIV-Negative AIDS'**

Most of those who claim to have 'HIV-Negative AIDS' tested positive for several types of pathogens. -China Daily/ANN

Sat, May 07, 2011

China Daily/Asia News Network

GUANGZHOU, China—Sixty people who had claimed they were suffering from a mysterious infectious condition dubbed "HIV-Negative AIDS" have been cleared of the disease, but 48 of them tested positive for several types of pathogens.

The research was done by a team of the No 1 Affiliated Hospital of the Guangzhou Medical University and the State Key Laboratory of Respiratory Disease, between March 31 and May 3.

Sixty patients, including 52 males, whose average age was 34.2 and who came from 16 provinces and municipalities, were examined, said Zhong Nanshan, director of the Guangzhou Institute of Respiratory Diseases, who directed the research.

The sufferers had shown symptoms for periods ranging from three months to 10 years.

Among the 48 who tested positive for pathogens, 33 tested positive for epidermolysis bullosa, 12 positive for chlamydia trachomatis (CT), nine for ureaplasma urealyticum (UU), seven for neisseria gonorrhoeae (NG), eight for cytomegalovirus and one for herpes simplex virus.

Sixteen tested positive for more than one of those pathogens, which are mostly related to sexually transmitted diseases.

In the 24 examined for knee diseases, 10 showed abnormalities in their knees, and in the 38 examined for eye diseases, 20 were diagnosed with conventional eye diseases. Twelve underwent psychological tests and seven were found abnormal.

Since 2009, media reports have stated that sufferers had displayed symptoms very similar to AIDS, such as swollen lymph nodes, subcutaneous bleeding, joint pain, fatigue, night sweats and emaciation.

The Ministry of Health stated in April that there was no evidence that those people were infected by the AIDS virus.

Wu Zunyou, an AIDS expert with the Chinese Center for Disease Control and Prevention, said no new viruses had been found among the alleged sufferers and they were most likely just suffering from a mental health problem often called AIDS phobia.

There is no fundamental difference between results of the research led by Zhong Nanshan and that by the Ministry of Health, said Hao Yang, deputy director of the bureau of disease prevention and control at the ministry, on Friday.

Zhong Nanshan said his team agreed with the ministry on the conclusions based on its research.

Many of the people involved in Zhong’s research had indulged in highly risky sexual behavior before showing the symptoms. Most of the pathogens were not detected with routine tests but with the more advanced fluorescent PCR tests, Zhong said.

Some sufferers had not received sufficient treatment before the research. With the number of AIDS cases increasing in China, the phobia over the disease has heightened, which has frustrated clinical treatments, Zhong said.

Lin Jun, a patient in the research project, said he had never thought he was infected with HIV but had been wrongly labeled as an HIV-Negative AIDS or AIDS phobia sufferer.

Lin said he was grateful for the research that confirmed he suffers from neisseria gonorrhoeae.

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**Coroners wrong to say no to post-mortem tissue collection, academics argue**

Monday, 9 May 2011

*The Coroner's Society "failed" in its duty to protect public health by refusing to take part in vCJD study*

The creation of a post-mortem tissue archive for a study of the human form of mad cow disease failed because of a "misguided" refusal by coroners to participate.

The Coroner's Society of England and Wales (CSEW) did not recognise its "moral obligation to protect public health" from potential new risks associated with variant Creutzfeldt-Jakob disease (vCJD) when it decided not to allow the collection of tissue from autopsies.

That is the conclusion of a paper co-written by a researcher at the London School of Hygiene & Tropical Medicine, which has been published online and is set to appear in a forthcoming edition of the journal Public Health.
The authors say they believe the reasons given by the CSEW were insufficient to justify not taking part in the study and call for a wider review of the role of coroners in future public health measures. They also criticise the move by the Government to abolish the proposed position of Chief Coroner as part of the Public Bodies Bill which is set to have its final reading in the House of Lords on Monday May 9.

Until 2003, all cases of vCJD—a fatal brain-wasting disease—in humans were caused by exposure to bovine spongiform encephalopathy (BSE) in the diet. More recently a small number of infections are thought to have resulted from blood transfusions from donors who did not know they were infected with vCJD. It is also believed that iatrogenic transmission may occur as a result of contaminated surgical instruments—a concern which prompted hospitals in Essex and Wales to contact patients earlier this year.

In response to the evidence that vCJD has the potential to emerge as a second-wave infection resulting from human-to-human transmission, the Health Protection Agency (HPA) attempted to create a post-mortem tissue archive.

Its aim was to determine the prevalence of abnormal prion protein, which is a marker for vCJD infection, in the UK in order to determine the efficacy of current precautionary measures and to determine if further measures might be necessary.

But following a protracted correspondence with the Chief Medical Officer, the CSEW declined to participate, citing issues including its legality, cost and feasibility, concluding that taking part would "adversely affect the independence of the coronial service and would further erode public confidence".

According to the authors of the paper, "declining to participate in this study was misguided and illustrates a considerable failure by the CSEW to recognise coroners' moral obligation to protect public health". They add: "The protection of public health is an appropriate and vital obligation of government officials as such protection helps to ensure the conditions necessary for individuals and groups to live healthy and safe lives."

Lead author Catherine McGowan, based in the Faculty of Public Health and Policy at LSHTM, said: "A Chief Coroner—one with a clear understanding of the role of the coroner's service in protecting the public good—should be able to facilitate this type of public health survey in the future."

"Despite the valiant attempts of the House of Lords to save the proposed position of Chief Coroner from abolition under the Public Bodies Bill, the position is now likely to be axed by the House of Commons. This seems a grave mistake."

**NIH study describes fast, sensitive blood test for human prion disease**

**WHAT:** Scientists from the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), report that they have developed a method—10,000 times more sensitive than other methods—to detect variant Creutzfeldt-Jacob disease (vCJD) in blood plasma. vCJD is a type of prion disease in humans that leads to brain damage and death. The NIAID researchers also used the test to rapidly detect scrapie, a prion disease of sheep, in infected hamsters, some pre-symptomatic.

Prion diseases, also known as transmissible spongiform encephalopathies, are difficult to diagnose, untreatable and ultimately fatal. Scientists believe disease-causing prions are abnormal infectious clusters of prion protein molecules. Normally, prion protein molecules exist in every mammal in an unclustered, harmless form. In prion diseases, tissue damage leaves microscopic sponge-like holes in the brain. Along with vCJD and scrapie, other forms of prion disease include chronic wasting disease in deer, elk and moose, and bovine spongiform encephalopathy, also known as mad cow disease.

Because animals and people can be infected for years before symptoms of disease appear, scientists have tried to develop a rapid and sensitive screening tool to detect prion diseases in blood, which would assist in efforts to prevent the spread of prion diseases among and between species, via the blood supply or otherwise.

Collaborating with scientists from Switzerland-based Prionics AG, the NIAID group combined an antibody-based approach with an improved real-time quaking-induced protein conversion (RT-QuIC) reaction. RT-QuIC, developed in recent years, detects when normal prion protein converts to an abnormal form (http://www.niaid.nih.gov/news/newsreleases/2010/Pages/prionCaughey.aspx). The resulting test—which they call enhanced QuIC (eQuIC)—improves prospects for routinely detecting low levels of abnormal prions in tissues, fluids or environmental samples such as soil. The group plans to study eQuIC as a potential tool to diagnose various prion diseases in different animals.

How Shifts in Temperature Prime Immune Response

ScienceDaily (May 7, 2011) — Researchers at The Scripps Research Institute have found a temperature-sensing protein within immune cells that, when tripped, allows calcium to pour in and activate an immune response. This process can occur as temperature rises, such as during a fever, or when it falls—such as when immune cells are "called" from the body’s warm interior to a site of injury on cooler skin.

The study, recently published online ahead of print by Nature Chemical Biology, is the first to find such a sensor in immune cells—specifically, in the T lymphocytes that play a central role in activation of killer immune cells. The protein, STIM1, previously known as an endoplasmic reticulum (ER) calcium sensor, had been thought to be important in immune function, and now the scientists show it is also a temperature sensor.

"Temperature has a profound effect on all biological processes including immune responses, but surprisingly little is known about molecules in immune cells that sense temperature shifts," said the study’s principal investigator, Scripps Research Professor Ardem Patapoutian. "Here we show that STIM1 senses temperature and has a profound impact on immune cells."

This is the second family of thermosensation molecules that the Patapoutian laboratory has uncovered. The team has isolated and characterized three of six members of the transient receptor potential (TRP) family of ion channels—the so-called thermoTRPs. "These proteins translate temperature, which is a physical stimulus, into a chemical signal—ions flowing into cells," said Patapoutian.

"ThermoTRPs mainly function in specialized sensory neurons that relay environmental temperature information to the brain."

In this study, the researchers turned to immune cells to look for temperature sensors. "Immune cells can experience dramatic temperature changes under either normal or pathophysiological conditions," said first author Bailong Xiao, a research associate in the Patapoutian laboratory. "The temperature drops significantly when, say, immune cells move from the 37 degree Celsius temperature of the spleen to skin, where it is normally 33 degrees. During fever, core body temperature can rise to 41 degrees." Scientists have discussed for decades whether fever is beneficial to the immune system. The researchers believe that identification of a molecular sensor of temperature within immune cells provides a novel avenue to address such questions mechanistically.

The research team, which included Bertrand Coste and Jayanti Mathur, also of the Patapoutian lab, found that STIM1 can be activated by heat with a high degree of temperature sensitivity. Both STIM1 and a plasma membrane pore-forming protein known as Orai1 have recently been identified as essential components of the so-called the calcium release activated calcium (CRAC) channel. But STIM1 had not been known to be heat sensitive until this research, according to Xiao.

The process goes like this: STIM1 proteins are located on the ER, which is the organelle that stores calcium inside the cell. When a sudden change in temperature occurs, STIM1 proteins cluster together and translocate close to the plasma membrane. There, these clusters then can activate Orai1, which leads to the opening of the channel pore and an influx of calcium to activate the cell. Calcium is essential for a number of cellular functions, and, in immune cells, a sustained influx of calcium into these cells activates gene expression and cell proliferation. It turns the immune cell "on," Xiao said.

The function of STIM1 and Orai1 had already been known to be critical to immune function, Xiao said. Mutations in genes encoding either of the proteins lead to development of severe combined immunodeficiency (SCID), the so-called "bubble boy" disease characterized by a complete absence of immunity.

Given the relatively wide expression pattern of STIM1, the researchers suggest that STIM1 may also function as a temperature sensor in other tissues in addition to immune system, including skin, brain, skeletal muscle, and even in blood platelets, all of which could experience moderate but significant temperature changes. For example, temperature-induced STIM1-mediated calcium influx may help muscle cells remodel after exercise, Xiao explained. "We know that calcium is very important for skeletal muscle physiology and remodeling. Temperature can rise in skeletal muscles when they are exercised."

The same principle may be working in blood platelets, where STIM1 is also found and plays important roles, he said. When platelets move to the skin surface to repair a cut, the change in temperature may activate STIM1, which can contribute to platelet activation, resulting in formation of a clot, Xiao said.

While sensing temperature is essential for survival and efficient metabolism, it is not clear yet if and how these findings can be clinically translated, said Patapoutian. "It is too early to make predictions on
the implications of these findings, but STIM1 and Orai1 are of interest to the pharmaceutical industry given their role in immunodeficiency.”

**Journal Reference:**
Bailong Xiao, Bertrand Coste, Jayanti Mathur, Ardem Patapoutian. **Temperature-dependent STIM1 activation induces Ca²⁺ influx and modulates gene expression.** Nature Chemical Biology, 2011; DOI: 10.1038/nchembio.558

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**Obese Teens Engage in Risky Behaviors Too— but in Sometimes Riskier Ways**

*Los Angeles Times*, (04.25.2011) Marissa Cevallos

A new analysis of federal data by psychologists at the Cincinnati Children’s Hospital Medical Center shows extremely obese teens are just as likely to engage in high-risk behaviors as their normal-weight peers.

Lead author Meg Zeller, an associate professor of pediatrics at the hospital, and colleagues used data from CDC’s 2007 Youth Risk Behavior Survey to compare the risky behavior of 410 extremely obese teens (body-mass index in the 99th percentile) with that of normal-weight teens (body-mass index within the 5th and 84th percentiles).

Extremely obese boys and girls had similar behaviors compared to their peers in terms of alcohol and drug use or having suicidal tendencies. Obese girls were less likely to have had sex than healthy-weight girls, though they were more likely to report drug or alcohol use before having sex, the study found. Obese and healthy-weight boys were as likely to have had sex before age 13, have had multiple partners or have used drugs or alcohol prior to sex.

Obese girls and boys were more likely to smoke cigarettes compared to their normal-weight peers. Obese boys were more likely to have started smoking before age 13, and obese girls were more likely to have tried cigarettes, be a current smoker, and to use smokeless tobacco.

“Given what we do know about what their day-to-day life is like, extreme obesity in particular being highly stigmatized, we expected that these teens would be more socially isolated and more peripheral in a peer group, and therefore less likely to be exposed to high-risk scenarios that a typical teen is exposed to,” said Zeller.


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**Ugandan Lawmakers Hold Hearings on Anti-Gay Bill**

*Associated Press*, (05.09.2011) Godfrey Olukya

Monday marked the second day of hearings by a Ugandan parliament committee on an anti-gay bill that has been condemned worldwide. The measure originally called for the death penalty for active homosexuals living with HIV or in cases of same-sex rape. Critics, including retired Anglican Bishop Christopher Senyonjo, said the bill could increase the spread of HIV/AIDS, since gay Ugandans would fear seeking treatment, and could turn the country into a police state. Under the measure, anyone who “aids, abets, counsels or procures another to engage in acts of homosexuality” would face seven years in prison. Landlords who rent out residences to gays could also receive seven years. The bill’s author, David Bahati, said the death penalty provision is “something we have moved away from,” and that a new version would likely be presented before a final vote, possibly this week. Some, all or none of these provisions could change during parliamentary negotiations, say lawmakers. Activists say the bill’s introduction has stoked the already deep, widespread anti-gay sentiment in Uganda.

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**Study Finds No XMRV-Chronic Fatigue Link**

***SUMMARY***
Analysis of blood samples from 300 people in Utah did not show an association between chronic fatigue syndrome and infection with XMRV retrovirus.

*By Liz Highleyman*

Some prior research has indicated that xenotropic murine leukemia virus-related virus (XMRV) and other murine leukemia virus (MLV) relatives are common in people with chronic fatigue syndrome (CFS), prostate cancer, and other conditions. CFS is characterized by overwhelming fatigue that does not improve with rest.

In particular, a study by Judy Mikovits from the Whittemore Peterson Institute and colleagues, published in the October 23, 2009, issue of Science, found that 67% of CFS patients had detectable XMRV in peripheral blood mononuclear cells, compared with just 4% of people without chronic fatigue.
These findings have led some CFS patients to use antiretroviral drugs developed for HIV on an off-label basis, and advocates have urged that clinical trials be started for this new patient population.

Study results have not been consistent, however, and other research teams have found no association between CFS and XMRV or related viruses.

In an effort to resolve this conflict, Clifford Shin and Ila Singh from the University of Utah and colleagues collected and analyzed blood samples from 100 CFS patients and 200 healthy volunteers from the Salt Lake City area, using molecular, serological, and viral growth assays. A majority (70%) of the CFS patients reported flu-like symptoms at the onset of fatigue, suggestive of viral infection.

As reported in the May 4, 2011, advance online edition of the Journal of Virology, the researchers did not detect XMRV or related MLVs, or antibodies against these viruses, in any of their patient samples. Furthermore, they also performed a blinded analysis of stored samples from CFS patients in the Mikovits study, but again found no evidence of XMRV infection.

"Our experience has taught us that the detection of XMRV in blood is fraught with difficulties," the researcher wrote, explaining that different laboratory techniques yielded conflicting results and suggesting contamination may play a role. Positive readings were initially obtained using a "biorobot," but when this equipment was abandoned XMRV was no longer detected.

"Given the lack of evidence for XMRV or XMRV-like viruses in our cohort of CFS patients, as well as the lack of these viruses in a set of patients previously tested positive, we feel that that XMRV is not associated with CFS," they continued. "We are forced to conclude that prescribing antiretroviral agents to CFS patients is insufficiently justified and potentially dangerous."

However, they added, "It is also vital to state that there is still a wealth of prior data to encourage further research into the involvement of other infectious agents in CFS, and these efforts must continue."

"Chronic fatigue syndrome is a devastating disease for which a cure needs to be found," Singh said in a press release issued by University of Utah Health Sciences. 5/10/11

**Reference**


### New Sepsis Discovery Goes Straight to the Heart to Save Lives

ScienceDaily (May 9, 2011) — New research published online in The FASEB Journal details research in rats and mice that offers hope for stopping the devastating, and often fatal, effects of sepsis in humans. In the study, University of Michigan researchers show how neutralizing the effects of a key protein fragment, called C5a, used by the immune system to attract white blood cells may ultimately prevent heart failure.

"During sepsis, heart failure is a common feature of the later stages of the syndrome," said Peter A. Ward, M.D., a senior scientist involved in the work from the Department of Pathology at the University of Michigan Health Systems in Ann Arbor, MI. "The current studies in experimental sepsis suggest that cardiomyocytes interact with the powerful complement-derived C5a anaphylatoxin, resulting in release of cardiopressive cytokines that may be linked with defective cardiomyocyte function developing during sepsis."

To make their discovery, Ward and colleagues obtained specialized heart muscle cells, called "cardiomyocytes" (CMs), from normal rats and incubated them in the laboratory with C5a. They found that the cardiomyocytes released specialized immune cells, called cytokines (IL-6 and TNF alpha), in a time-dependent and dose-dependent manner. Sepsis was also induced in mice, and CMs isolated from these mice and examined in vitro. The scientists found that these cells spontaneously released a variety of cytokines, several of which appeared to have the potential to harm the heart. When other mice with beginning stages of sepsis were injected with an antibody to neutralize C5a, the activity of the heart-harming cytokines was reduced. Furthermore, when mice bred to lack receptors for C5a were subjected to sepsis, little or no spontaneous release of cytokines from heart cells occurred.

"Under the best circumstances, sepsis is unpredictable and difficult to treat," said Gerald Weissmann, M.D., Editor-in-Chief of The FASEB Journal, "It's perhaps the most serious problem in emergency medicine and when sepsis affects the heart it moves from serious to grave. Now that we know that C5a is at least partly responsible, antibodies to C5a promise to get to the heart of the problem."

According to the National Institute of General Medical Sciences, NIH, Sepsis is a major challenge in the intensive care unit, where it is one of the leading causes of death. It is caused when immune chemicals released into the blood to combat infection trigger widespread inflammation, resulting in impaired blood flow, which damages the body’s organs by depriving them of nutrients and oxygen. In the worst cases, the heart weakens and multiple organs—lungs, kidneys, liver—may quickly fail and the patient can die. Each
year, severe sepsis strikes about 750,000 Americans, and as many as half die, which is more than the number of U.S. deaths from prostate cancer, breast cancer and AIDS combined.

**Journal Reference:**

**Scientists Unmask Mysterious Cells as Key 'Border Patrol Agents' in the Intestine**
ScienceDaily (May 9, 2011) — Researchers at UT Southwestern Medical Center have uncovered new clues about how the intestine maintains friendly relations with the 100 trillion symbiotic bacteria that normally live in the digestive tract.

Their latest findings, available online in the *Proceedings of the National Academy of Sciences*, suggest that a once enigmatic cell population which lurks in the intestinal lining is essential for preventing friendly bacteria from invading into deeper tissue where they can cause debilitating conditions like inflammatory bowel disease (IBD).

"Possible new therapies for IBD could be devised by learning how to boost the antibacterial functions of this particular group of cells," said Dr. Lora Hooper, associate professor of immunology and senior author of the study. "The findings also might help researchers better understand how probiotics — mixtures of beneficial bacteria that are added to food products — boost the immune system."

The human intestine is home to a staggering number of bacteria. These microorganisms are put to good use as metabolic workhorses that help to liberate nutrients from the diet for our uptake and use.

While most healthy people have a friendly relationship with their gut microbes, this relationship turns sour in patients battling IBD. People suffering from the disease frequently have more bacteria that adhere to or invade their gut lining. When their immune system mounts an attack on these microbial invaders, they can develop painful ulcers and bloody diarrhea.

For this study, researchers studied mice genetically engineered to lack a mysterious immune cell called a gamma delta intraepithelial lymphocyte (γδ IEL). This specialized T cell is found at body surfaces such as the skin and the gastrointestinal tract, where it insinuates itself between the epithelial cells that line these surfaces. These cells make up a large proportion of the body's T cells, but their exact function had been unclear.

"Our findings suggest that a major function of these T cells is to patrol intestinal borders, sensing when microorganisms have invaded the epithelial cells lining the intestine," said Dr. Hooper, who is also an investigator for the Howard Hughes Medical Institute at UT Southwestern. "When this happens, these T cells swing into action, making antibiotic proteins that kill the rogue bacteria and prevent their entry into deeper tissue."

The researchers also found γδ IEL cells play an important role in preventing intestinal pathogens such as *Salmonella* bacteria from spreading to deeper tissues.

"These T cells manifest their importance in the first three to four hours after the pathogen is encountered. This suggests that their primary responsibility may be to 'hold down the fort' until other immune cells can be recruited as backup," Dr. Hooper said.

**Journal Reference:**

**Diet, exercise and cancer screening boosted by 'highly feasible' intervention targeted at HIV serodiscordant couples**
Michael Carter
Published: 11 May 2011
Fruit and vegetable consumption and exercise frequency can be increased by participation in a health promotion intervention designed to reduce the risk of chronic diseases, investigators report in the April 25th edition of the *Archives of Internal Medicine*.

The research involved African-American HIV-serodiscordant heterosexual couples who were randomised to receive either information and motivation about the benefits of good diet and exercise, or a general HIV/sexual health promotion intervention.

Up to a year after completing the programme, couples participating in the healthy living intervention were significantly more likely to report eating a diet rich in fresh fruit and vegetables and regular exercise.
Moreover, participation in the enhanced health promotion information was associated with the consumption of less fatty food, and increased rates of screening for prostate and breast cancer. “The present results demonstrate that a health promotion intervention had significant effects on multiple health behaviors in African-American HIV-positive and HIV-negative individuals,” comment the investigators. The author of an accompanying editorial was “particularly impressed with the intervention.”

Chronic conditions such as cardiovascular disease are now an important cause of illness and death in people with HIV. Therefore, addressing modifiable risk factors for such illnesses is now an important priority of HIV care.

African-Americans represent 48% of all HIV-positive patients in the US, and African-Americans generally eat fewer fruit and vegetables, exercise less frequently, and have poorer survival rates for prostate and breast cancer than white Americans.

Investigators therefore wished to see if an intervention could improve a range of health behaviours in HIV-serodiscordant African-American couples enrolled in an HIV/sexual health promotion study.

The study was conducted between 2003 and 2007. The intervention consisted of eight two-hour weekly sessions and was designed to build skills and knowledge about eating lots of fruit and vegetables, exercise, the reduction of fat in diet, screening for prostate and breast cancer, and alcohol use.

A total of 550 individuals were randomised to receive the intervention, and 520 individuals were randomised into a control arm, and received HIV/sexual health information. Outcomes were monitored six and twelve months after completion of the trial.

At baseline, only 21% of participants overall reported eating five or more portions of fruit and vegetables a day, and fewer than 20% exercised regularly.

Six and twelve months after completing the study, individuals in the intervention arm were 38% more likely than those in the control arm to report having a diet that incorporated large amounts of fruit and vegetables (odds ratio [OR] = 1.38; 95% CI, 1.18-1.62, p < 0.001). Patients in the intervention arm were also significantly less likely to report the consumption of fatty foods (p = 0.003).

They were also 39% more likely to report regular exercise (OR = 1.39; 95% CI, 1.22-1.59, p < 0.001). Rates of prostate and breast cancer screening were also significantly higher in the intervention arm (p < 0.001 and p = 0.009 respectively).

However, alcohol consumption was comparable in the two arms of the study. The investigators speculate that this was because individuals in the control arm received information about the role of alcohol in HIV risk behaviour.

“We are optimistic that the present study offers an approach that may help reduce the disproportionately high morbidity and mortality rates from chronic diseases in African-Americans,” conclude the authors.

In his accompanying editorial, Dr Mitchell H. Katz of the Los Angeles Department of Health described the intervention as “highly feasible”, adding that although it was conducted in serodiscordant couples, “there is no reason to believe that [the] intervention would not work among HIV-infected persons.”

Reference

Johnson & Johnson Unit Finds Traces of Fungicide in HIV Drug

Reuters, (05.11.2011) Esha Dey

Regulatory agencies in the United Kingdom, Canada, Ireland, Germany, and Austria are working with a J&J unit to address trace amounts of a fungicide found in the HIV drug Prezista in their respective markets. Janssen said it initiated the investigations into the five lots after it received four complaints of a musty, moldy odor in Prezista. The odor was likely caused by trace amounts of tribromoanisole (TBA), a fungicide used in packing materials, found in bottles sourced from a common supplier, Janssen said in a statement. Though a very small number of patients reported temporary gastrointestinal symptoms, there were no reports of serious adverse advents related to TBA, the company said. TBA has been linked to many of J&J’s recalls over the past year and a half.
New Insect Repellant May Be Thousands of Times Stronger Than DEET

ScienceDaily (May 10, 2011) — Imagine an insect repellant that not only is thousands of times more effective than DEET—the active ingredient in most commercial mosquito repellants—but also works against all types of insects, including flies, moths and ants.

That possibility has been created by the discovery of a new class of insect repellant made in the laboratory of Vanderbilt Professor of Biological Sciences and Pharmacology Laurence Zwiebel and reported this week in the online Early Edition of the Proceedings of the National Academy of Sciences.

"It wasn't something we set out to find," said David Rinker, a graduate student who performed the study in collaboration with graduate student Gregory Pask and post-doctoral fellow Patrick Jones. "It was an anomaly that we noticed in our tests."

The tests were conducted as part of a major interdisciplinary research project to develop new ways to control the spread of malaria by disrupting a mosquito’s sense of smell supported by the Grand Challenges in Global Health Initiative funded by the Foundation for the NIH through a grant from the Bill & Melinda Gates Foundation.

"It's too soon to determine whether this specific compound can act as the basis of a commercial product," Zwiebel cautioned. "But it is the first of its kind and, as such, can be used to develop other similar compounds that have characteristics appropriate for commercialization."

The discovery of this new class of repellant is based on insights that scientists have gained about the basic nature of the insect’s sense of smell in the last few years. Although the mosquito's olfactory system is housed in its antennae, 10 years ago biologists thought that it worked in the same way at the molecular level as it does in mammals. A family of special proteins called odorant receptors, or ORs, sits on the surface of nerve cells in the nose of mammals and in the antennae of mosquitoes. When these receptors come into contact with smelly molecules, they trigger the nerves signaling the detection of specific odors.

In the last few years, however, scientists have been surprised to learn that the olfactory system of mosquitoes and other insects is fundamentally different. In the insect system, conventional ORs do not act autonomously. Instead, they form a complex with a unique co-receptor (called Orco) that is also required to detect odorant molecules. ORs are spread all over the antennae and each responds to a different odor. To function, however, each OR must be connected to an Orco.

"Think of an OR as a microphone that can detect a single frequency," Zwiebel said. "On her antenna the mosquito has dozens of types of these microphones, each tuned to a specific frequency. Orco acts as the switch in each microphone that tells the brain when there is a signal. When a mosquito smells an odor, the microphone tuned to that smell will turn "on" its Orco switch. The other microphones remain off. However, by stimulating Orco directly we can turn them all on at once. This would effectively overload the mosquito's sense of smell and shut down her ability to find blood."

Because the researchers couldn’t predict what chemicals might modulate OR-Orco complexes, they decided to "throw the kitchen sink" at the problem. Through their affiliation with Vanderbilt's Institute of Chemical Biology, they gained access to Vanderbilt's high throughput screening facility, a technology intended for the drug discovery process, not for the screening of insect ORs.

Jones used genetic engineering techniques to insert mosquito odorant receptors into the human embryonic kidney cells used in the screening process. Rinker tested these cells against a commercial library of 118,000 small molecules normally used in drug development. They expected to find, and did find, a number of compounds that triggered a response in the conventional mosquito ORs they were screening, but they were surprised to find one compound that consistently triggered OR-Orco complexes, leading them to conclude that they had discovered the first molecule that directly stimulates the Orco co-receptor. They have named the compound VUAA1.

Although it is not an odorant molecule, the researchers determined that VUAA1 activates insect OR-Orco complexes in a manner similar to a typical odorant molecule. Jones also verified that mosquitoes respond to exposure to VUAA1, a crucial step in demonstrating that VUAA1 can affect a mosquito’s behavior.

"If a compound like VUAA1 can activate every mosquito OR at once, then it could overwhelm the insect’s sense of smell, creating a repellant effect akin to stepping onto an elevator with someone wearing too much perfume, except this would be far worse for the mosquito," Jones said.

The researchers have just begun behavioral studies with the compound. In preliminary tests with mosquitoes, they have found that VUAA1 is thousands of times more effective than DEET.

They have also established that the compound stimulates the OR-Orco complexes of flies, moths and ants. As a result, "VUAA1 opens the door for the development of an entirely new class of agents, which
could be used not only to disrupt disease vectors, but also the nuisance insects in your backyard or the agricultural pests in your crops," Jones said.

Many questions must be answered before VUAA1 can be considered for commercial applications. Zwiebel’s team is currently working with researchers in Vanderbilt's Drug Discovery Program to pare away the parts of VUAA1 that don’t contribute to its activity. Once that is done, they will begin testing its toxicity.

Vanderbilt University has filed for a patent on this class of compounds and is talking with potential corporate licensees interested in incorporating them into commercial products, with special focus on development of products to reduce the spread of malaria in the developing world.


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**Beneficial Bacteria Help Repair Intestinal Injury by Inducing Reactive Oxygen Species**

ScienceDaily (May 11, 2011) — The gut may need bacteria to provide a little bit of oxidative stress to stay healthy, new research suggests.

Probiotic bacteria promote healing of the intestinal lining in mice by inducing the production of reactive oxygen species, researchers at Emory University School of Medicine have shown.

The results, published online this week in *Proceedings of the National Academy of Sciences* Early Edition, demonstrate a mechanism by which bacterial cultures in foods such as yogurt and kimchi have beneficial effects on intestinal health. The insights gained could also guide doctors to improved treatments for intestinal diseases, such as necrotizing enterocolitis in premature babies or intestinal injury in critically ill adults.

The laboratories of Andrew Neish, MD and Asma Nusrat, MD, both professors of pathology and laboratory medicine, teamed up for the study. The paper’s co-first authors are postdoctoral fellow Philip Swanson, PhD and associate research professor Amrita Kumar, PhD.

"It’s been known for years that probiotic bacteria can have these kinds of helpful effects, but it wasn’t really clear how this worked," Neish says. "We’ve identified one example, among many, of how certain kinds of bacteria have specific biochemical functions in the body."

Recent research has shown that the bacteria in our intestines influence our metabolism and immune systems. For example, an imbalance in the proportions of harmful and beneficial bacteria seems to over-activate immune cells in the intestines, driving inflammatory bowel disease.

Intestinal epithelial cells, the cells that line the intestine, live in close contact with bacteria and normally form a barrier that keeps bacteria away from other organs. They can repair small gaps in the barrier, which breaks down in intestinal diseases, by migrating into the gaps.

The researchers showed that *Lactobacillus rhamnosus* bacteria can accelerate this healing process, both in culture dishes and in mice with intestines damaged by chemicals. *Lactobacillus rhamnosus*, a species of bacteria found naturally in human intestines and often used as a probiotic, is a relative of other kinds of Lactobacillus bacteria found in fermented foods.

"Unlike most cell types that can not tolerate bacterial contact, intestinal epithelial cells respond to *Lactobacillus rhamnosus* by increasing their motility," Neish says.

Using a fluorescent dye that is sensitive to reactive oxygen species (ROS), the researchers showed that intestinal epithelial cells produce ROS internally when in contact with *Lactobacillus rhamnosus*. The ROS induced by the bacteria stimulate the formation of focal adhesions, structures on intestinal epithelial cells that act as anchors for their movement.
"Focal adhesions are where cells attach to the matrix that surrounds them," Neish says. "The cells lay them down on one side and remove them on the other side, like the tracks of a bulldozer."

In studying the effect of *Lactobacillus rhamnosus* on intestines in mice, Neish’s team focused on the small intestine, which normally has fewer bacteria than the colon. This allowed them to avoid using antibiotics to remove naturally existing bacteria beforehand, and to see ROS production in tissue from live animals.

Antioxidants that mop up ROS prevent the bacteria from promoting wound healing in the laboratory, the researchers showed. Neish says his team’s finding suggests that large amounts of antioxidants by humans could interfere with the ability of bacteria to promote intestinal healing.

Previously, it was known that immune cells respond to bacteria by producing ROS, but Neish and his colleagues believe the ROS production they observed stimulates tissue maintenance and is a marker of cohabitation and adaptation, rather than defense.

Oxidative stress, or an imbalance of reactive oxygen species throughout the body, has been linked to diseases such as heart disease and stroke. However, scientists have learned in recent years that cells can also use reactive oxygen species in a controlled, local way to send signals needed for normal functions.

Neish says his team is working to determine which part of the bacteria is responsible for inducing cells to produce ROS. Once identified, this component could be used to encourage intestinal healing in situations where contact with large amounts of live bacteria might be dangerous, such as in premature babies or critically ill adults.

**Journal Reference:**


NYTimes, May 12, 2011

**Early H.I.V. Therapy Sharply Curbs Transmission**

By DONALD G. MCNEIL JR.

People infected with the virus that causes AIDS are far less likely to infect their sexual partners if they are put on treatment immediately instead of waiting until their immune systems begin to deteriorate, according to preliminary results from a large clinical trial released Thursday.

Patients with H.I.V. were 96 percent less likely to pass on the infection if they were taking antiretroviral drugs — a finding that is so overwhelming that it is likely to change the way American AIDS doctors treat patients and what treatment policies are adopted by the World Health Organization and other countries, said Dr. Anthony S. Fauci, head of the National Institute of Allergy and Infectious Diseases, which paid for the trial.

The data was so convincing that the trial, scheduled to last until 2015, is effectively being ended early.

There have been previous studies, notably among drug abusers in San Francisco and Vancouver, British Columbia, that concluded that starting patients on drugs immediately would stop them from infecting others.

Those studies led U.N.AIDS, the United Nations AIDS-fighting agency, to adopt “test and treat” as its goal last year; the policy encourages doctors to start people on treatment as soon as they test positive for H.I.V. However, this is the first evidence from a randomized clinical trial, the gold standard in medical research.

AIDS prevention specialists not connected to the trial were enthusiastic.

“These results are phenomenal,” said Thomas J. Coates, director of the global health program at the University of California, Los Angeles, and the founder of the Center for AIDS Prevention Studies in San Francisco. “It was a tough study to do, and I’m thrilled it came out this way.”

Dr. Julio Montaner, an AIDS specialist at the University of British Columbia whose work among Vancouver heroin addicts helped lead to the U.N.AIDS policy, called the result of 96 percent protection “as good as it gets.”

“This is consistent with what we’ve been saying and doing in British Columbia for close to a decade,” he said. “How much more evidence do we need before we implement what we know works?”

The $73 million trial, known as HPTN 052, involved 1,763 couples in 13 cities on four continents. One member of each couple was infected with H.I.V.; the other was not. In half the couples, chosen at random, the infected partner was put on antiretroviral drugs as soon as he or she tested positive for the virus.

In the other half, the infected person started treatment only when his or her CD4 count — a measure of the immune system’s strength — dropped below 250 per cubic millimeter.
In 28 of the couples, the uninfected person became infected with the partner’s strain of the virus. Twenty-seven of those 28 infections took place in couples in which the partner who was infected first was not yet getting treatment.

On Thursday, Dr. Fauci and Dr. Myron Cohen, an AIDS specialist from the University of North Carolina at Chapel Hill and the study’s director, announced that the data collected since the study began in 2005 had been “unblinded” to an independent safety review panel, which is standard procedure in clinical trials. When the panel realized how much protection early treatment afforded, it recommended that drug regimens be offered to all participants. Although participants will still be followed, the trial is effectively over because it will no longer be a comparison between two groups on different regimens.

The results carry moral implications for doctors in the United States. Although medical associations like the Infectious Diseases Society of America advocate starting patients on AIDS drugs early, the decision is made by the doctor and patient. Some patients fear the reported side effects of AIDS drugs and want to delay taking the drugs until they get obviously sick or until their CD4 counts fall, and some doctors go along with that, Dr. Fauci said, especially as long as their patients’ CD4 counts remain above 350.

But that means the patient may infect others during the delay. Of the 27 people in the study who became infected while their partners were not yet taking the drugs, 17 had partners whose CD4 counts were still above 350.

Asked if it could now be considered immoral for a doctor to accede to a patient’s request to delay starting drugs, Dr. Fauci said: “I’m not going to go there. I’m not going to say it’s immoral. But there is more and more data showing the advantages of starting as early as you can.”

Dr. Coates of U.C.L.A. said he hoped that treatment delays would fade away because the newest antiretroviral drugs had few side effects.

Although the evidence suggests that it would be good public health policy to lower infection rates by starting everyone on drugs as soon as they are infected, that is impossible in much of the world. For lack of money, clinics in Africa are turning away patients who are not just infected but close to death. And in some American states where money provided by the Ryan White Care Act has run out, poor uninsured people are on waiting lists.

Although the trial was relatively large, there are some limitations on interpreting the data.

More than 90 percent of the couples in the trial, who lived in Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, the United States and Zimbabwe, were heterosexual.

“We would have liked to have a substantial number of men as potential study subjects, but they just weren’t interested,” Dr. Cohen said.

Although common sense suggests the results would be similar in the contexts of homosexual sex and sex between people who are not couples, strictly speaking, the results apply only to the type of people studied, Dr. Fauci said.

**Progress on HIV treatment ‘fragile’, says MSF report**

Keith Alcorn
Published: 12 May 2011

Although major strides have been made in achieving access to antiretroviral treatment in low and middle-income countries, progress is fragile and highly vulnerable to diminishing attention from donors, Medecins sans Frontieres says in a new report published ahead of next month’s United Nations General Assembly Special Session on AIDS.

The report also highlights progress towards implementation of 2009 World Health Organization guidelines in 16 countries that represent half the global burden of HIV infection.

The guidelines include recommendations that countries shift towards providing earlier treatment, and adopt less toxic first-line drug regimens.

The survey found that 12 of 16 countries have either shifted to recommending earlier treatment, or are likely to do so shortly.

First-line treatment with d4T ( stavudine) was the norm when countries began to scale up antiretroviral treatment in the early 2000s because the drug was cheap and easy to coformulate in fixed-dose combinations. Over time it has become clear that a high proportion of patients suffer unacceptable levels of toxicity as a result of taking this drug, and WHO has recommended using tenofovir or AZT instead.
However, changes in first-line treatment that would result in the use of tenofovir, a less toxic drug, have been implemented in only half of the countries. In the remainder national guidelines now recommend AZT, which although less toxic than d4T, still causes some long-term side effects. AZT is cheaper than tenofovir.

The survey also found that almost all countries have opted to implement the cheaper of two optional regimens for prevention of mother to child HIV transmission. The World Health Organization has recommended that at a minimum, either pregnant women should receive three-drug antiretroviral therapy until the end of the breastfeeding period, or they should receive short-course prophylaxis with two drugs. Only two countries have chosen to adopt the triple-drug protocol.

While some countries have already achieved fairly good treatment coverage for those who need it, seven of the 16 countries in which MSF works are still unable to provide treatment to more than 40% of people with CD4 counts below 350. While Zambia is already able to provide treatment to 68% of people who need it, and Kenya and Ethiopia to around half, only 32% of eligible patients are receiving treatment in Mozambique, and 37% in South Africa.

Medecins sans Frontières says that this year's UN meeting on AIDS is very important as it will possibly be the last meeting of its kind for years to come and may therefore shape the response to the HIV epidemic for the next five to ten years.

"Today, ten million people are in urgent need of treatment," says Dr Tido von Schoen-Angerer, Executive Director of MSF's Access Campaign. "We know so much more from the past decade about how to get treatment to as many people as possible as quickly as possible. With the right policies in place, we could triple the number of people on treatment without tripling the costs. But if governments don't support a treatment target, they are sending a clear message that they do not intend to ever come to grips with this pandemic."

### Alarming HIV-prevalence stats

**YNGVE SJOLUND—May 13 2011 15:34**

About 50% of black gay men or men who have sex with men (MSM) in Soweto are living with HIV. Research statistics from the Global Forum on MSM and HIV estimates that HIV prevalence among the black gay male community of the township is four times higher than the general population.

Dr Michael Laurino from the Health4Men Clinic at Baragwanath Hospital in Soweto says research in South Africa shows that African men having sex with men are a particularly vulnerable group, specifically those living in peri-urban informal settlements.

The forum is the only global HIV and Aids advocacy network specifically devoted to the needs of men who have sex with men. Various studies indicate the prevalence of HIV among gay men in South Africa is between 10.4% and 33.6%. As a result, men who have sex with men have been identified by the government and major donors for targeted health interventions intended to decrease the impact of the virus on this group.

Nthato Ramushu, a nurse at the Health4Men Clinic, says it is fighting against high rates of HIV and sexually transmitted infections among these men in Soweto and other areas around the country. "The term MSM is quite new for many people and because same-sex sexuality is easily misunderstood, this group is often neglected in HIV prevention and treatment campaigns. Almost half of the men living in Soweto who are gay or are MSM won't say they are gay or identify themselves to anyone as gay," he says.

According to Ramushu, men who have sex with men in all communities have specific needs in terms of healthcare and access to health services. He says they are also known to be at a higher risk of HIV infection and transmission. "There is approximately 5% of men in South Africa having sex with other men and HIV prevalence among these men in townships like Soweto is estimated to be between 30% and 50%," says Ramushu.

David Motsagea, an outreach coordinator for the Health4Men Clinic, says informal talks in the community revealed that alcohol and multiple concurrent partners are major influences on the high level of HIV in Soweto. "Feedback from the community showed most gay people and men who have sex with men are desperate and find themselves in a community of Africans where they are not accepted. Most people's understanding of men who have sex with men in the township is that it means a man is gay. Education has been needed to show people that other groups fall under the category of MSM," he says.

According to Motsagea, a man who is still in the "closet" is at greater risk of being exposed to HIV because he can have only secret relationships, during the night. "This man, referred to as an 'after-nine',
will engage in 'quickies', which means he may not have a condom with him and there is a greater chance he and his partner are exposed to the HI virus."

Motsagea says men who are attracted to men sometimes marry women because they want to conform to society's expectations and have a wife and children. "It happens often in the community where the clinic lies, because males have to do what their parents tell them to do and live according to societal expectations. So it is very difficult for young people who get pressured to get married and have a family but are attracted to men," he says.

Big issues among black people about being gay are stigma and acceptance. "For African men to come out and say 'I am gay or MSM' or 'I prefer to have sex with men' can lead to their parents disowning them since it is considered not acceptable. Other issues of independence, manhood and power struggles continue to be predominant problems."

Motsagea says that for previous generations it was difficult to discuss sexuality, but today parents have information from print media and television that allows them to be open. "Only now do men have the platform to talk. Before, if someone was MSM or thought they were gay, they would have to conform to their parents' expectations. A difference can be seen now where people are starting to accept those who are MSM because of access to information."

Laurino says the MSM population at the clinic is aware of HIV and using condoms and that sexually transmitted infections such as gonorrhoea relate to sexual activity without using a condom. "HIV is a generalised condition and sometimes people don't see the link that HIV is a sexually transmitted disease. Everyone talks about HIV but don't seem to make the psychological link that it is sexually transmitted because it is a condition that affects the whole body, not just the genital area. Genital conditions are more obvious and visible as a sexually transmitted disease."

The message to use condoms is out there but people do not always want to use them because of a lack of knowledge. "Many HIV-infected couples feel they can continue not using condoms because they are HIV positive anyway. What they don't realise is that they are reinfecting each other with the disease over and over and should always wear condoms," says Ramushu.

Because men who have sex with men were identified as a target group needing health intervention to reduce HIV rates, the Health4Men project was launched in Cape Town in 2009. It was the first of its kind to provide an easy location for men to take steps against sexually transmitted and HIV infections and offer men's wellness services in the Western Cape, Gauteng and North West.

Approximately 3 200 patients have been helped through its outreach work and through attendance at the Soweto clinic. The actual number of people managed with antiretrovirals on a regular basis is about 2 500.

"Men who are considering having sex with other men—or are occasionally having sex with men—can go to the clinic to discuss concerns and anxieties and can get help managing their health in terms of their HIV status and screening for sexually transmitted infections. It is a safe space that is confidential and easily accessible," says Laurino.

Yngve Sjolund is a consultant for various HIV/Aids NGOs, writing and editing research material about HIV, sexual and reproductive rights, gender-based violence and sexual minorities. This article was made possible through funding from the Open Society Foundation of South Africa's media fellowship programme.

Source: Mail & Guardian Online

HIV Treatment Dramatically Reduces Sexual Transmission

**SUMMARY**

Early antiretroviral therapy (ART) decreased the likelihood of HIV transmission between heterosexual partners by 96% in the large international HPTN 052 trial.

By Liz Highleyman

Effective combination antiretroviral treatment usually reduces HIV RNA to a low or undetectable level, and people with a low viral load are much less likely to transmit the virus. This has been conclusively demonstrated for mother-to-child HIV transmission, and new findings confirm that it applies to sexual transmission as well.

HIV Prevention Trials Network (HPTN) Study 052 is a large Phase 3 clinical study, sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), looking at the effects of early ART on HIV transmission risk.
Myron Cohen from the University of North Carolina at Chapel Hill and colleagues enrolled 1763 serodiscordant couples—almost all of them heterosexual—in 9 countries (Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, U.S., and Zimbabwe) starting in 2005. Couples were about evenly divided between those with an HIV positive woman and those with an HIV positive man; past research has shown that HIV is more easily transmitted sexually from male to female than vice versa.

At the time of enrollment the HIV positive partners had CD4 T-cells counts between 350 and 550 cells/mm³—above the recommended threshold for treatment initiation at the start of the trial. (U.S. treatment guidelines now recommend starting when the CD4 count falls to 500 cells/mm³.)

HIV positive participants were randomly assigned to either start a 3-drug antiretroviral regimen immediately or defer treatment until their CD4 count fell below 250 cells/mm³ or they developed an AIDS-related illness. Participants used various combinations made up of 11 different drugs. In addition, people in both groups received safer sex counseling, free condoms, regular HIV testing, and screening and treatment for other sexually transmitted infections.

Results

- HIV positive men and women who started ART early were significantly less likely to transmit the virus to their sexual partner.
- An interim analysis found 39 cases of HIV infection among previously negative participants, 28 of which were genetically linked to their regular HIV positive partner.
- Of these 28 linked infections, only 1 occurred among couples in the immediate ART arm, compared with 27 in the deferred treatment group.
- Based on these numbers, immediate ART reduced the risk of HIV transmission by 96.3%.
- Furthermore, 17 cases of extrapulmonary tuberculosis occurred among HIV positive partners in the deferred treatment arm compared with just 3 cases in the immediate ART arm, a statistically significant difference.
- The number of deaths was similar, however, with 10 in the immediate ART arm and 13 in the deferred treatment group.

HPTN 052 was originally designed to end in 2015, but an independent Data and Safety Monitoring Board recommended that the study should be halted and results released ahead of schedule after an interim review showed that immediate ART substantially reduced HIV transmission risk. HIV positive partners in the deferred treatment arm will now be offered ART and participants will be followed for at least a year.

"The results are the first from a major randomized clinical trial to indicate that treating an HIV-infected individual can reduce the risk of sexual transmission of HIV to an uninfected partner," according to a NIAID press release.

Previous observational studies and mathematical models have indicated that early ART could reduce transmission, but these new findings from a "gold standard" randomized trial provide stronger evidence.

"This new finding convincingly demonstrates that treating the infected individual—and doing so sooner rather than later—can have a major impact on reducing HIV transmission," said NIAID Director Anthony Fauci. He added in a media briefing that HPTN 052 "nails the concept down."

In 2008 the Swiss Federal Commission for HIV/AIDS sparked controversy when it issued a statement saying, "An HIV-infected person on antiretroviral therapy with completely suppressed viremia...is not sexually infectious." The commission emphasized that the statement only applied to vaginal intercourse between heterosexual partners in which neither had other sexually transmitted infections and the HIV positive person had a stable undetectable viral load on ART for at least 6 months.

A number of researchers have reported rare cases of HIV transmission from individuals on ART with undetectable viral load, however, and many clinicians and advocates have argued that it is irresponsible to suggest that people on treatment can safely engage in unprotected sex.

Since HPTN 052 almost exclusively enrolled heterosexual couples, its results cannot be applied to men who have sex with men. There is good reason to expect that lowering viral load will reduce transmission in this population as well, but similar controlled studies are needed to show the magnitude of risk reduction.

The latest findings will further inform the ongoing debate about treatment as prevention. These data lend support to "test and treat" proponents who believe everyone who tests HIV positive should begin treatment right away, both for their own health and for the public health benefit of reducing transmission.
In early 2010 the San Francisco Department of Public Health and San Francisco General Hospital were the first to adopt a policy of offering immediate ART to everyone diagnosed with HIV.

Others, however, feel that the long-term effects of antiretroviral agents are not yet fully understood, and argue that concerns about drug resistance, lifelong adherence, and cost weigh in favor of a more cautious approach.

"With these results we should redouble our efforts to diagnose individuals with HIV earlier," said HIV Medicine Association Chair Kathleen Squires in a press release issued by HIVMA and the Center for Global Health Policy. "We now have further evidence that effective treatment not only benefits the individual but also will help reduce the spread of this disease."

"This rigorously conducted clinical trial demonstrates that ART dramatically reduces HIV transmission from an infected partner to an uninfected spouse or partner," concurred HPTN investigator Sten Vermund from Vanderbilt University in a Family Health International press release. "Earlier therapy is a superior option that benefits both an infected individual and his or her uninfected partner and we support global efforts to offer ART to everyone who needs it." 5/13/11


Sources

Study finds pigs susceptible to virulent ebolavirus can transmit the virus to other animals

[EMBARGOED FOR MAY 13, 2011] Canadian investigators have shown that a species of ebolavirus from Zaire that is highly virulent in humans can replicate in pigs, cause disease, and be transmitted to animals previously unexposed to the virus. The findings are published in The Journal of Infectious Diseases and are now available online. (Please see below for a link to the embargoed study online.)

In order to prevent human outbreaks of Ebola hemorrhagic fever, it is important to identify animal species that replicate and transmit the virus to other animals and, potentially, people. Zaire ebolavirus, one of several species of the virus, has a fatality rate as high as 90 percent in humans. Antibodies to another species not associated with human disease, known as Reston ebolavirus, have been found in pig farmers in the Philippines, suggesting pigs may be able to transmit virulent ebolavirus to humans as well.

This study, led by Gary P. Kobinger, PhD, of the Special Pathogens Program, National Microbiology Laboratory, Public Health Agency of Canada, and Hana Weingartl, PhD, of the National Centre for Foreign Animal Disease at the Canadian Food Inspection Agency, investigated whether Zaire ebolavirus, like Reston ebolavirus, could replicate and cause disease in pigs and be transmitted to other animals. Using domesticated pigs, the researchers first evaluated virus replication, pathogenicity, and shedding. Following mucosal exposure to Zaire ebolavirus, the pigs replicated the virus in high amounts, mainly in the respiratory tract. Shedding of the virus from nasal mucosa was detected for up to 14 days post-infection, and severe lung disease was observed. The study also showed that the virus was transmitted to all previously unexposed pigs co-habiting with the infected animals.

The study authors suggest that domesticated pigs are susceptible to Zaire ebolavirus through mucosal infection and that the pigs' accompanying severe respiratory disease is associated with shedding of high viral loads into the environment, exposing uninfected pigs to the infection. In contrast to the systemic syndrome affecting multiple organs that often leads to shock and death in primates, they noted, the respiratory syndrome that develops in pigs could be mistaken for other porcine respiratory diseases.

In an accompanying editorial, Daniel G. Bausch, MD, MPH & TM, of the Tulane School of Public Health and Tropical Medicine in New Orleans, noted that the study's findings raise important questions for additional research on ebolavirus. The results described in the study are "cause for consideration, for further scientific study" but are not cause for panic, Dr. Bausch wrote.

Fast Facts:
1. Zaire ebolavirus, one of several species of ebolavirus, has a fatality rate as high as 90 percent in humans.
2. Antibodies to Reston ebolavirus, a species of the virus not associated with disease in humans, have been found in pig farmers in the Philippines.
3. In this study, pigs exposed to Zaire ebolavirus became infected and transmitted the infection to previously unexposed pigs.

**Scientists design new anti-flu virus proteins using computational methods**

One goal of antiviral protein design is to block molecular mechanisms involved in cell invasion and virus reproduction.

A research article May 12 in *Science* demonstrates the use of computational methods to design new antiviral proteins not found in nature, but capable of targeting specific surfaces of flu virus molecules. One goal of such protein design would be to block molecular mechanisms involved in cell invasion and virus reproduction.

Computationally designed, surface targeting, antiviral proteins might also have diagnostic and therapeutic potential in identifying and fighting viral infections.

The lead authors of the study are Sarel J. Fleishman and Timothy Whitehead of the University of Washington (UW) Department of Biochemistry, and Damian C. Ekiert from the Department of Molecular Biology and the Skaggs Institute for Chemical Biology at The Scripps Research Institute. The senior authors are Ian Wilson from Scripps and David Baker from the UW and the Howard Hughes Medical Institute.

The researchers note that additional studies are required to see if such designed proteins can help in diagnosing, preventing or treating viral illness. What the study does suggest is the feasibility of using computer design to create new proteins with antiviral properties.

"Influenza presents a serious public health challenge," the researchers noted, "and new therapies are needed to combat viruses that are resistant to existing anti-viral medications or that escape the body's defense systems."

They focused their attention on the section of the flu virus known as the hemagglutinin stem region. They concentrated on trying to disable this part because of its function in invading the cells of the human respiratory tract.

Their approach was somewhat similar to engineering a small space shuttle with the right configuration and construction, as well as recognizance and interlocking mechanisms, to dock with a troublesome space station and upset its mission. Only these scientists attempted their engineering feat at an atomic and molecular level.

Central to their approach is the ability of biological molecules to recognize certain other molecules or their working parts, and to have an affinity for binding to them at pre-determined locations. This recognition has both physical and chemical bases. Protein-protein interactions underlie many biological activities, including those that disarm and deactivate viruses.

In their report, the researchers described their general computational methods for designing new, tiny protein molecules that could bind to a certain spot on large protein molecules. They took apart some protein structures and watched how these disembodied sections interacted with a target surface. They analyzed particular high-affinity interactions, and used this information to further refine computer-generated designs for interfaces.

"Protein surfaces are never flat, but have many crevices and bulges at the atomic scale," lead author Sarel Fleishman explained. "The challenge is to identify amino acid side chains that would fit perfectly into these surfaces. The fit must be precise both in shape and in other chemical properties such as electrostatic charge. This geometrical and biophysical problem can be computationally solved, but requires large computational resources."

The researchers made use of a peer-to-peer computing platform called Rosetta@Home for going through the hundreds of millions of possible interactions of designed proteins and the surface of hemagglutinin to solve this challenge.

Following optimization, the designed proteins bound hemagglutinin very tightly.

Through this method, the researchers created two designs for new proteins that could bind to a surface patch on the stem of the influenza hemagglutinin from the 1918 H1N1 pandemic flu virus.

The shortcomings of the approach, due to approximations, meant that the researchers started out with 73 possibilities of which just two were successful.

One of the disease-causing characteristics of the influenza hemagglutinin stem is that it changes shape by refolding when in an acidic environment. This reconfiguration appears to allow the virus reproduce itself inside of cells.
In this study, one of the newly designed proteins was shown to block a conformational change, not only in H1 influenza hemagglutinin, but also in a similar component in H5 avian influenza.

"This finding suggests that this new protein design may have virus-neutralizing effects against multiple influenza subtypes," the researchers reported.

What was unusual about the workable designs was that they had helical binding modes, roughly shaped like a spiral staircase, rather than the loop binding that naturally occurring antibodies employ.

X-ray crystallography of the proteins complex showed that the actual orientation of the bound proteins was almost identical to the way the binding mode was designed. The modified surface of the main recognition helix on the designed protein was packed into a groove on the desired region of the virus protein.

"Overall, the crystal structure is in excellent agreement with the designed interface," the researchers noted, "with no significant deviations at any of the contact points." The design and the actual formation were nearly identical.

The scientists were encouraged by this finding. Despite their limitations, the design methods, the scientists believe, capture the essential features of the desired protein-protein interaction.

**Bacterium Found to Kill Malaria in Mosquitoes**
ScienceDaily (May 13, 2011) — Researchers at the Johns Hopkins Bloomberg School of Public Health have identified a bacterium in field-caught mosquitoes that, when present, stops the development of *Plasmodium falciparum*, the parasite that causes malaria in humans. According to the study, the Enterobacter bacterium is part of the naturally occurring microbial flora of the mosquito's gut and kills the parasite by producing reactive oxygen species (or free radical molecules). The study is published in the May 13 edition of *Science*.

"We've previously shown that the mosquito's midgut bacteria can activate its immune system and thereby indirectly limit the development of the malaria parasite. In this study we show that certain bacteria can directly block the malaria parasite's development through the production of free radicals that are detrimental to *Plasmodium* in the mosquito gut," said George Dimopoulos, PhD, senior author of the study and associate professor at the W. Harry Feinstone Department of Molecular Microbiology and Immunology, and the Johns Hopkins Malaria Research Institute.

"We are particularly excited about this discovery because it may explain why mosquitoes of the same species and strain sometimes differ in their resistance to the parasite, and we may also use this knowledge to develop novel methods to stop the spread of malaria. One biocontrol strategy may, for example, rely on the exposure of mosquitoes in the field to this natural bacterium, resulting in resistance to the malaria parasite."

Like humans, mosquitoes have a variety of bacteria in their digestive systems. For the study, the researchers isolated the Enterobacter bacterium from the midgut of Anopheles mosquitoes collected near the Johns Hopkins Malaria Research Institute at Macha, which is located in southern Zambia. About 25 percent of the mosquitoes collected contained the specific bacteria strain. Laboratory studies showed the bacterium inhibited the growth of *Plasmodium* up to 99 percent, both in the mosquito gut and in a test tube culture of the human malaria parasite. Higher doses of bacteria had a greater impact on *Plasmodium* growth.

Worldwide, malaria afflicts more than 225 million people. Each year, the disease kills nearly 800,000, many of whom are children living in Africa.

**Journal Reference:**

By Megan Scudellari

**Proteins on the prowl**
Defensive proteins kill bacteria invading mouse cells by delivering deadly sacs of antimicrobial chemicals
[Published 5th May 2011 06:00 PM GMT]
Researchers have identified the function of an obscure but large family of proteins whose function in cellular immune responses had been unknown.
Guanylate-binding proteins, Gbps for short, protect cells from pathogens that have snuck into a cell by activating cellular degradation machinery, according to a study published today (May 5) in Science. Understanding how the proteins work could help spur the development of small drug molecules to activate a cell's own defenses against infection, a potential alternative to antibiotics.

"The function of the Gbps remained mysterious for a very long time despite the fact that they are produced in massive amounts upon infection," said Sascha Martens, who studies autophagy at the Max F. Perutz Laboratories in Austria and was not involved in the research, in an email to The Scientist. The new findings "could be a breakthrough in the field of resistance to intracellular bacterial pathogens."

Gbps are produced in abundance in response to type II interferon, a defense activation protein released by host cells in presence of pathogens. John MacMicking and colleagues at the Yale University School of Medicine performed a loss of function screen on the 11 members of the Gbp family, individually silencing the RNA transcripts of the genes in mouse macrophages. "Now that we can target RNA, it allows us to discriminate between individual members of a closely related family," said MacMicking.

The researchers found that four of the Gbps—Gbp1, Gbp6, Gbp7, and Gbp10—conferred immunity to two bacteria: Listeria monocytogenes, responsible for food borne infection in humans, and Mycobacterium bovis, a close relative to the bacterium that causes tuberculosis. Engineering Gbp1-deficient mice, the team confirmed that animals lacking the Gbp1 gene were more susceptible to infection.

Digging into the mechanism by which the proteins protect the cells, the researchers found that at least two of them, Gbp1 and Gbp7, deliver antimicrobial cargo such as toxic peptides to the bacteria in sac-like vesicles (see below video). Gbp1 also tags invading bacterial cells so that they are delivered to lysosomes and digested.

The team conducted additional experiments in human cells and found that human orthologs of the Gbp proteins also help fight infection. "It looks like there's conservation across both human and mouse, and we anticipate there will be conservation across other vertebrate species as well," said MacMicking.

Understanding how the cell's internal defensive machinery works could help scientists develop small molecule drugs that imitate its ability to fight and kill bacteria. "We're running out of new antibiotics," said MacMicking. "One idea is to eventually generate drugs that actually mimic host processes that are normally very effective at clearing bacteria."


By Laura J. Snyder

**Wanted: Another Scientific Revolution**

*In the 19th century, four friends changed the way scientists viewed themselves. It’s time for another shake-up.*

When H.M.S. Beagle set sail from Plymouth Sound on December 27, 1831, the ship's young naturalist, Charles Darwin, was a self-proclaimed "natural philosopher." By the time he disembarked the ship about five years later, he was a "scientist"—a word invented in the intervening years by fellow Cambridge University alum and polymath William Whewell.

Much else had changed as well. Whewell and a group of his friends had begun to modernize the concept of the natural philosopher, a project first hatched in 1812, when they met as undergraduates at Cambridge University.

Each of the four men was brilliant, self-assured, and possessed of the optimism of the age: Whewell, who later created the fields of mathematical economics and the science of the tides; Charles Babbage, a mathematical genius who would invent the prototype of the first modern computer; John Herschel, who mapped the skies of the Southern hemisphere and coinvented photography; and Richard Jones, a curate who went on to shape economic science. The four composed what I call the "Philosophical Breakfast
Club,” also the title of my latest book, which chronicles the way they transformed the “man of science” into the professional scientist.

At “Philosophical Breakfasts” held on Sundays after compulsory chapel services, the four students cast their young, critical eyes over science as it was then practiced, and found it wanting. They pledged to bring about nothing less than a scientific revolution—and in large part they succeeded.

Because of these men, science was transformed from the province of the amateur—the clergyman collecting fossils or beetles in his spare hours, or the wealthy gentleman conducting electrical experiments at his country estate—to the career of the professional: trained at the university, published in specialized journals, and admitted to associations open only to fellow professionals.

Darwin’s career was thus framed by the revolution brought about by these men. But he was also influenced more directly by the members of the Philosophical Breakfast Club. At Cambridge from 1828 to 1831, Darwin attended John Henslow’s botany lectures with Whewell, who—probably during their strolls to the class—suggested that Darwin read his friend Herschel’s new book, A Preliminary Discourse on the Study of Natural Philosophy, which appeared the month that Darwin was taking the exams necessary to complete his degree.

Herschel’s book, aimed at a popular audience, promoted Francis Bacon’s inductive, evidence-based scientific method. “Scarcely anything in my life made so deep an impression on me” as the book, Darwin later wrote to Herschel. “It made me wish to try to add my mite to the accumulated store of natural knowledge.” In short, it sparked Darwin’s transformation from amateur naturalist into scientist.

One of the unintended consequences of the revolution wrought by the Philosophical Breakfast Club has been that the professional scientist is now less interested in, and perhaps less capable of, connecting with the broader public, sharing the new discoveries and theories that most excite the scientific community. Although there are some notable exceptions, today’s researcher has been less adept than the Victorian-era natural philosopher at engaging the public—and this estranged the general public from science. In part this is because the scientific establishment discourages its members from writing popular books and articles, considering these projects unserious, even frivolous, diversions from the real work of research. But this attitude has to change in order to mend the ever-deepening rift between science and the rest of modern culture. Today’s scientist should strive to be more like the 19th-century natural philosopher—ironically, more like those very men who created the modern scientist.

An expert on Victorian science and culture, Fulbright scholar Laura J. Snyder served as president of the International Society for the History of Philosophy of Science in 2009 and 2010. She is associate professor of philosophy at St. John’s University, in New York City, and also the author of Reforming Philosophy: A Victorian Debate on Science and Society. An excerpt from her new book can be accessed here.

comments

To Chris
by anonymous poster, [Comment posted 2011-05-09 23:15:57]

Among the most unfortunate problems with quotes of celebrities is that they represent only one aspect of a highly nuanced context. Another is that the quoiter almost always has an agenda in citing a quote that was not the agenda of the person quoted. Feinman indicated once (no need for his exact words) that a few hours spent by a student in trying to come up with an original idea, is worth far more than the same number of hours spent in memorizing what someone else already has figured out.

Feinman did, indeed, rely heavily on transforms in attempting to explain concepts relating to conversions of matter to energy, and you do well to appreciate them.

If you like transforms (transformations) you will love Fourier’s. Just as one of Gilbert’s models did in regard to electricity, Fourier’s transforms enabled calculations relating to how heat behaves, without attempting to demonstrate what heat is. And nothing in thermodynamics actually does any better. Dictionary definitions can be made up, based upon how things behave, or what they do, without ever revealing what they “are.” A bogdesaloresor is a zordeltic demalportal. We know as much about a bogdesaloresor as we do about what light is, or heat, or magnetism, or the spin or color of a quark, or whether our (or the) universe is seamless or grainy.

We call things laws that we cannot test to confirm. Try finding a place where the vector of an object is conserved in a vacuum if no outside force acts upon it. Where do we find a place where there is no outside force upon an object? Try to create a perfect vacuum and strange things begin to happen in the container. If light is in a vacuum, it is not a vacuum.

All the thousands of things we humans perceive ourselves to be able to observe and measure, can be reduced to seven (See SI Units). And we do not know, actually, what any one of the seven actually is. We do have much evidence that those seven tend to scale up or down somewhat proportionately from one frame of reference to another.

Being the reader you are, you know what a fallacy it is, in the minds of those who think science deals only with material things (matter and energy). If we make a rule that we will not treat as science anything we cannot test, we rule out First Principles and Laws said to be self-evident. Self-evident is code for “we cannot test it, but agree to mutually ASSUME IT without question.”

To first make a rule that nothing is valid in science unless it can be tested, rules out Newton’s Third Law (as suggested above) and numerous other presumptions relied upon in scientific “work” every day.

But, of course, all your reading in lieu of TV watching, has led you to the realization of these mysteries already.

A. Jeenious

To In-Jeenius.
by Chris Cox, [Comment posted 2011-05-09 13:06:36]

You posted this quote:
There are lots and lots of things I don’t know. However, I can tell you what I think. I won’t take offense if you tell me what you think, even if I feel very, very strongly that you are wrong. I think the odds are very good that I’m right. But let’s see what evidence turns up in the future.

Richard Feynman?

I just received his "QED in New Zealand" DVD but haven’t had a chance to view it.

I agree with MS Snyder. We need popularizers of science in the vein of Sagan, Feynman, Kaku and others. Writers like Lincoln Barnett who’s book, "The Universe And Dr. Einstein"(1957ed.), first introduced me to the Lorentz Transformation equation when I was in high school, can explain in laymen’s terms the concepts scientists are working on. I was probably one of only a few students in that high school in East Tennessee who would have bought such a book. Most of my friends were more interested in cars and the opening of squirrel season. Introduction to science has to start in first grade.

It would also appear to my uneducated mind that a major blow to interest in science started in the ‘50's with the acquisition of televisions by almost everybody, and the immediate proliferation of televangelists, a group of admittedly science-hostile believers.

Chris "Kit" Cox

*Untrusted & Marginalized*  
by Bruce Carnes, [Comment posted 2011-05-09 11:35:14]

The final step of the Scientific Method is to let others know the results of our work. This conversation has been and continues to be extended to the general public through vehicles like Scientific American, Science Friday on NPR, television programs like NOVA and by such amazing communicators as Stephen Jay Gould in their books.

The longer we scientists remain hidden behind the walls of academia, the more our profession will be mistrusted and marginalized.

I would go even further and suggest that our profession has an obligation to communicate with the public. It is not credible to me that our work, regardless of its complexity, cannot be translated into images and words that can be understood by people without scientific training. It does not reflect well on us if it cannot.

In the absence of this conversation, how can we create and inspire the next generation of scientists?

*Again, stop this stupid nonsense!*  
by Ruth Rosin, [Comment posted 2011-05-09 05:31:50]

In a previous message I examined the problem scientists would face if expected to explain their most complex scientific work to the general public.

Let’s now look at the problem from the point of view of the general public.

We’ll have to assume that the general public would be interested in seriously studying science (as well as the history, sociology and psychology of science), at the level of undergraduate and graduate college-courses, and that members of the general public would be able to afford devoting time to that, even though they usually need to work to support themselves, and their family (if they have one), and may prefer spending their free time in many other ways, shopping, watching light entertainment on television, playing computer-games, engaging in sports, chatting with friends, partying, devoting time to serious activities other than science, and much more; or just having a good time. You could not force such a general public to devote time to scientific enlightenment.

On top of all that, science has by now become so vast, and often so highly specialized, that scientific experts in one field of science, rarely understand what is happening in other scientific field. But the general public is expected to be prepared to understand all scientific fields.

Be realistic!

*The total knowledge management of the life (TQM-L)*  
by Alexandru Cosciuc, [Comment posted 2011-05-08 14:36:47]

A very interesting point of view!

be British company ESRC start up in 2009 a similar action but only for the small literary creation. The known sculptor Constantin Brancusi said: “the humanity can be saved by the art; the artist made the toys for the adults”.

Human resources to produce information may be defined as the total knowledge and integrating knowledge management in the life quality is a desire manifested by the German philosopher and mathematician Leibniz in his known “the certitude method”. Descartes method of doubt is today known as the virtual faults configuration and is used as a management tool in the virtual flow chart strategies. Identifying weaknesses before the action of the natural or artificial feedback is the main purpose of the TQM, called “zero fault”.

The accumulated operational knowledge during the entire human life can be assimilated with the management system design. We can recall worker’s debate participation, known in the management as the brainstorming, as the soul and brain storming if we use the artistic capacity of the science man.

Encouraging the science man to produce literature or another kind of the art can be a strategy to reach zero faults in the life quality.

I will visit very soon your site!

*Knowing and Method*  
by Alec Schauer, [Comment posted 2011-05-08 03:50:44]

It is fairly obvious that explaining the complex findings of science to the public at large is problematic. But this aspect too is beside the point when viewing all interconnections. At any time in history most explorers were so engrossed in their view that they thought their findings were utterly important and could not easily be explained to others. A few centuries or even decades later they were utterly put into new perspectives. The really relevant point is not in the results, but in the methods, which can at times be utterly off track concerning a complete understanding, but can be utterly attractive to the vast majority of scientists and financing politicians—for example because they provide gadgets for manipulating materials, as is the case today. A capacity in this direction does not necessarily mean that this kind of scientists really understand the nature of matter, but only that they can manipulate it very cleverly. Even some animals can manipulate matter according to their expectations. But this is no proof of anything like a complete understanding ? and as mentioned the point is in method, while the nature and principles of method can indeed be explained, even in school or to the public at large. Yet one of the deep problems today is that scientists and even many philosophers do not bother about a complete understanding of their subject matter; most prefer to believe that it is an impossible endeavor. But if that were true, then their assertive suggestion could not be true since it stems from an incomplete understanding and can thus not ensure its own validity. So the essential question remains and is worth being pursued. As mentioned in my earlier posts, it is by far not as unpromising as the average scientific mind must believe.
Stop this stupid nonsense!
by Ruth Rosin, [Comment posted 2011-05-07 23:07:21]
The idea that a scientist should explain his most complex science to the general public is a beautiful utopian dream, perfectly feasible in theory, and utterly impossible in practice. Assuming that we are dealing with a literate general public, that is well-versed in everything taught about science in pre-college courses (which is usually not at all the case), the scientist would have to teach that general public everything he learned about science, and used in his work, in college, starting from the first college degree and continuing through graduate school. The scientist should, of course, not undertake to reach all that himself, or he would never be able to do any more science, but send the general public to college to study all the necessary course-work. He should, then, send the general public to study all the science books and publications, he had himself learned from, after obtaining a graduate, and possibly, post-graduate training. Ten, or twenty years after he starts from scratch his project to educate the general public, he can attempt to explain his most complex scientific work to this general public.

Only those scientists who cannot see how utterly stupid this whole idea is, need to try and implement it. I suspect that they cannot be very good scientists in the first place. But I wish them the best of luck!

Science without humanity?
by MADHU THANGAVELU, [Comment posted 2011-05-07 13:56:19]
Great article!
I agree that modern scientists need to do much more to communicate their findings to a much, much broader audience. This helps not only in the efficient flow of knowledge, but serves a much more practical purpose. Besides inspiring a new generation of thinkers and doers, communicating findings in an inspiring way attracts the attention of potential sponsors from the most unlikely fields of endeavor, not to mention philanthropists from around the globe.
Yes, many of the concepts are hard to put into words that inspire for the layman, but then that’s the rub, I suppose? I like to think that media like dynamic webpages, Youtube and mass marketing portals, while taboo for the traditional "aloof" traditional personality of the serious scientist, is fast finding a prominent niche in the good lab worker's portfolio.
Good and skillful communications and marketing stoke the "fire in the belly" of active researchers, and the feedback from non-traditional sources bring fresh insight to imaginative and creative minds working on difficult problems, while simultaneously helping fetch megabucks to the table.

One of the great sins of our time, as Mohandas Gandhi aptly phrases in his autobiography is doing "Science without Humanity", and perhaps modern tools allows us to open up our minds to the world in ways never before possible.

For more on these topics...
by Laura Snyder, [Comment posted 2011-05-07 08:16:55]
I am blogging about related topics on my website at www.laurasnyder.com and on Facebook at www.facebook.com/authorlaurasnyder, for any who are interested in joining in the discussion there!

Further Thoughts....
by Laura Snyder, [Comment posted 2011-05-07 08:10:29]
Thank you all for your interest and thoughtful comments! I would just like to add a couple of quick points. I do not mean to suggest that each and every working scientist must make the effort to communicate his/her results to the general public. However, I do feel that one problem in our society today is a pervading scientific illiteracy; few in the general public know, or even care to know, about scientific developments that will, inevitably, be influencing our lives in the coming decades. The public education system in our country must play a role in fixing this problem, obviously. But also the scientific community should do more to raise awareness of science among the public (and not only scientists, also members of my field, the history and philosophy of science, can help do this as well). Otherwise, we are leaving a big gaping hole of ignorance that certain ideologues are more than happy to fill. Think of what happened with "intelligent design." Evolutionary biologists felt, a bit understandably, squeamish about "debating" the merits of evolution with creationists in the light of the public press, and this allowed the creationists to make inroads they would not otherwise have been able to make.

As for the point about a "typically Anglocentric" view of science in the 19th century: in THE PHILOSOPHICAL BREAKFAST CLUB, I do compare the situations in England, France and Germany in the early 19th century. The fact that England seemed to be falling behind in the area is partly what motivated the four members of the group to revolutionize science in England; I also argue that parts of their transformation of "the scientist" then filtered back to the Continent as well.

The Art of Knowing Everything
by Alec Schaerer, [Comment posted 2011-05-07 05:06:35]
Thank you dear anonymous In-Jeeno person for once more reminding the scientific community that the Art of Knowing Everything starts with knowing fully oneself and hence one’s way with dealing with the universe. Indeed, even a barmaid can understand this. She might even understand that this means understanding fully one’s own way of thinking while actually thinking. Concerning the principle this is merely a question of being interested in the topic? while the realization of this principle is a question of a mental discipline that few want to venture into. They prefer to talk endlessly and often arrogantly about reality ‘out there’ as if that was the essence of reality. Yet the reality to address is totality in it’s complete sense—for example the observed plus all of the observer and his conceptual and hence mental activity, before starting to expound predicates about the world ‘out there’. I pointed out as an essential point in a post yesterday (2011-05-06 13:19:07) that on the one hand concepts are formed via experience, and then on the other hand they constitute the means for steering one’s action and selecting further experiences. Humans should (and could) understand the fully self-referential character of their way of being, and then they can easily understand the fully self-referential character of reality in it’s complete sense, as it appears in statements such as ‘actio=reactio’ in classical mechanics or entanglement and non-locality in the quantum approach. Level-headed and open-minded barmaid understand in a fully self-referential way, they are keenly aware of human traits—which is why they can deal with men as efficiently as they do?

Explaining science
by anonymous poster, [Comment posted 2011-05-06 22:45:24]
Not to show any disrespect for greatness and celebrity, but let us dare to question a quote attributed to the late great Dr. A. Einstein, indicating one does not understand something unless he can explain it so as to be understood by a barmaid. More correct in my humble estimation are the words of Lincoln Barnett, written in the 1950s, to the effect that... as technology allows us to probe phenomena farther and farther beyond the reach of our meager senses, as the data they provide access to presents more contradictions, as concepts are stretched thinner and thinner to reach around those data... our findings and our efforts to make...
sense of them become ever more remote from human experience. (Not a direct quote, but the jist of it.) If there is a barmained somewhere out there in the night to whom can be explained the significance of how light travels at the same speed in each frame of reference, but is not the same for an observer inside a given frame of reference as for an observer in any other... and a bar patron who can find the words to communicate that to her with clarity, let me take my hat off to each.

Or, take microbiology's recent evidence that a retransposeon, in happening to land next to a gene, though it be methylated, may be released from methylation, along with that gene, and thence alter the timing or the degree or the rate of that gene's expression, not only in germ line cells but also in somatic cells and, not only prior to or during gestation or maturation, but at any time in an organism's life... but that only accounts for how some mutations may occur, and not how any can account for knocking down the odds against a BENEFICENT phenomenon. It helps to explain why identical twins and clones of complex eukaryotes differ, but it still falls short of leading us to a mechanism yet to be discovered whereby a species may come up with a "challenge-appropriate" mutation, as opposed to a deleterious one, as opposed to a random INAPPROPRIATE one. Who knows? Maybe a year from now, or a decade, or a century from now, someone will come up with hard evidence to show that retransposesons gravitate, at some statistically significant rate, more toward genes correlating to specific environmental stresses, or food availability niche changes, than to random landing sites. There has to be such a mechanism, or all the IMPLICIT wording of states making species "adapt" might suggest to our precocious barmained that we KNOW of, and can EXPLAIN, the mechanism, or the set of mechanisms, that enable a species to INTERACT with its environment in a proactive way. We do NOT know of any such mechanisms. And no evidence, nor testable model to date has given us an inkling of what how the ODDS allow that any species should come up with "situational stress appropriate" mutations that solve problems such as not having a heavy enough coat of hair, when an ice age begins. What are the odds that random chance would not come up with myriad inappropriate mutations, and just not that one that is needed.

Explaining a model that has been invented to explain the data and observations and experimental results we DO have, to date, is NOT the same as coming up with THAT data. And if, when that is pointed out to a microbiologist his response is to accuse the "messenger" that the messenger is too naive and too stubborn to accept that the model is "obvious"... Is that a scientific response? How refreshing it would be if no scientist would pretend he/she knows MORE THAN HE/SHE ACTUALLY KNOWS!

Wouldn't that be a great way to break the ice and start an objective dialog.

We know a lot. But we don't know EVERYTHING quite yet. And any explanation that begins with how things appear to be shaping up, rather than styled as an accounting for "how things are," or "how things work," would be... what... an admission of weakness? An insult to ourselves and all others seeking answers?

Could it be that there is a lot of glossing over, a lot of bigotry, a lot of chauvinism going on that, yes, even a barmained might see through... even if her IQ is not at the top of a bell-shaped curve.

Could it be that the first step in being honest with others is to begin being honest with ourselves?

Our brightest and best minds but push the edges of an envelope constrained by our lack of ability to experience all that is, directly or indirectly, and our lack of ability to recognize EVERY pattern in the universe (or multi-verses, even if it bops us in the nose).

Yes, we have come a long way, we humans, in a mere blip in time. But how far have we not yet gone?

How many of us have the intellectual courage to admit how limited we are, and how much we rely upon best guesses to explain even what we know?

Just explain it so outsiders can understand?

That'll work. Just as soon as we have enough pieces of many puzzles to come up with an explanation we can understand, ourselves.

A. Jeenious

Lost: my post of an already started revolution removed?
by Shi Liu, [Comment posted 2011-05-06 19:49:31]
I posted the following comment earlier: Such a Revolution Has Already Been Started See the links below:
LINK
LINK
However, my post was removed. Why?

Sure ... want a revolution...
by Mike Breeden, [Comment posted 2011-05-06 14:54:00]
The point of science is to explain things. If you don't communicate them, what success is that?
I wrote an amazing book, to describe an entirely new philosophy based on Darwinian principles. It was brilliant, revolutionary and inaccessible. I understood that, so I took advantage of the media of the day. See what I did. Offer an opinion. PastToTheFuture.com.
I think I explained things that demand explanation and I have more that might explain things you never thought could be explained.

Getting our own house in order
by anonymous poster, [Comment posted 2011-05-06 14:52:49]
Although not in a science profession, I deem myself to be a supporter of science— not science as a bastion from whence current consensuses must be defended vigorously against their detractors, but science as a perpetually self-upgrading coping tool of humanity, and as the enemy of dogma for dogma's sake. (Dogma for sake of trying to make sense of what lies BEYOND empirical testing is nothing more than pure fuzzy thinking at work toward arriving ultimately at rigorous testable thinking. Most advances in science have grown out of what was once pure speculation and fuzzy rationalization.)
The enemy of science is dogmatic insistence on a current model, as if to prevent its disparagement by an enemy of "truth." And thus the enemy is not merely the riff raff ranting outside the gates of research but, also, the enemy WITHIN, qua those who too enthusiastically and too successfully disparage any opinion but their own.

Does that happen? Read blogs among people in the science schools and professions and see for yourself.)

Openness to adopting a working hypothesis, for sake of some baseline from which results may be evaluated from a standard view is both practical and necessary; but insisting upon the presumption that any other hypotheses is automatically nonsense, is a phenomenon to be pondered. Taking alternative rationales off the back burner and treating them as inimical to reason, or protesting against monetary support for them, is historically established folly. Does anybody actually exercise such squelching? Well, there are some who believe their perception of reality is all in that set who believe that anything any evidence or reasoning outside that perception is, well..., not worth wasting time on. But, if you look around without blinders... see for yourself.
No sense of "loyalty" on part of any "scientist" to any current model hastens the day when that model will be, as it must, replaced by another that fits future data better. And, granted, every possible alternative rationale can’t be funded. But some projects are categorically denied funding, on grounds they would test things the reviewer knows are a waste of time. What if the reviewer is biased? Wait a century. Maybe then...

Meanwhile, who is the greater enemy of scientific progress? Is it the intractable disbeliever who never saw the inside of a laboratory, or took a microscope to the field, and objects to a current model on grounds it fails to comply with his/her untestable dogmatic beliefs? Or is it the intractable science-literate, objector against any alternative line of research that don’t fit his/her not-yet-tested predilections about where progress is headed?

From the amount of emotion directed at any untestable beliefs that do not conform to an insider’s OWN untestable beliefs... it would seem that a shouting match is underway between one individual’s untested, or untestable beliefs, and another’s. And then, when scientists want the public to know that they do have hard evidence for or against a particular thing, is it any wonder that the public—conditioned to expect heated opinions of untestable things—is not sure the evidence is really there?

The history of scientific progress is a trail marked not by compliance with the current wisdom of one’s time, but by upendings of conventional wisdom apple carts. Saying so is not intended to take away from the reality that it is the rank and file of researchers, plodding away at their work benches, or diggings, or super-collider squiggles, or whatever... trying to find data to support existing hypotheses, and FAILING, who lay the groundwork for some darned synthesis to come along and, as it were, build a new city on the ruins of the old.

Some articles in peer reviewed publications, as well as more, perhaps, in pop-science publications, seem to hold that it is necessary to fight fire with fire, and argue with non-scientist detractors in an emotional way, lest some hypothesis about something they cannot prove or disprove, other than their own, make its way into a schoolroom. Doing so, however, pits their own beliefs about

Does learning a lot about a given subject, better qualify a person to know things he can neither prove nor disprove? Some seem to think so.

In every age, some of the best minds have fallen into the trap of protesting too much against any assumption that would tend to insult that day's veritas accomplii (sp.)? A common fallacy, by the great thinkers of any time, seems to be that their culture has ARRIVED, if not at a point from which ultimate truth may be known then, at least, at a point from which the direction and height of the p[i]nnacle are predictable.

Has today's conventional wisdom done something that of no prior age achieved? If so, it’s the first time in history. And, if history is any indicator of probability, then probably not. In fact, not only do we not yet know everything, but we probably don’t have a clue where empirical evidence goes from here.

How adamant were Euclidean geometers that there was only one geometry, before it was realized another better explains certain phenomena, and that these could co-exist without the one contradicting what another can apply to.

Ever have a kid in the back seat asking, "Are we there yet?"

Nope, not yet.

Could it be that one reason non-scientists of Earth today might wonder if some experts are objective is because some of them (and some pop-science writers) have hotly treated their own personal predilections as self-evident (as dogma).

Well, this old SUPPORTER of science, believes research should be as open as it can be to things that cannot be rule out nor in, and avoid getting steamed or hostile if the unfalsifiable ideas of another conflict with their own unfalsifiable opinions.

Maybe revolution is not the right word for letting forthcoming evidence lead the way, and letting data speak for itself.

There is an attitude that fits this old f-t’s idea of what is science at its highest and best; and that attitude is:

"There are lots and lots of things I don’t know. However, I can tell you what I think. I won’t take offense if you tell me what you think, even if I feel very, very strongly that you are wrong. I think the odds are very good that I’m right. But let’s see what evidence turns up in the future."

Aw shucks! That'll never happen.

But, hey, it was a nice thought while it lasted. (=>)

A. Jeenious

**The Medium is the Message**
by John Toeppen, [Comment posted 2011-05-06 13:47:49]

Science is currently presented to the public on television on PBS, Discovery, and the Science channel. If we think that the public will read white papers we are delusional. Mass media is the most effective way to educate the public in science as well as the only effectively way to accomplish education on a global scale. Between You Tube and HDTV there are great new venues for modern science and we would be blind to not embrace this trend. Infotainment is the trend for public science and is also the core of any passionate scientific pursuit (we enjoy the intellectual engagement induced by exposure to new information).

Scientists need to engage in social entrepreneurialism if we want to change the world for the better. The world would be a far better place if people were to use scientific methods to evaluate their choices. Religion and politics depend on assumptions, and we are all too familiar with the results of that approach. If we could get people to realize that our assumptions are merely hypothesis we would be better off. Or we could remain content with mediocrity and complain about the consequences of our own inactions and inability to excite people about science and our options for the future.

**Natural History is moving back to the public**
by David Hill, [Comment posted 2011-05-06 13:38:55]

The old style of Natural History, so popular in the 1850-1950 time frame, is re-emerging in the arena of amateur observers. This is the result of two trends. First, new technology such as digital video and photography in concert with the internet, allows the serious amateur to disseminate original observations quickly, to a world-wide audience with common interests. Second, formal institutions have largely abandoned this area of inquiry, and formal publications in the area are stilted because of a professional need to turn all observations of nature into a "model system" for the investigation of some "extremely important" principles of nature. Related obfuscation can challenge the thinking, and the enjoyment, of the serious amateur. Amateurs are more common today that you think.

Many professionals, for example, do their amateur work on the side.

**Scientific revolution vs. objective conceptual evolution**
by Alec Schaerer, [Comment posted 2011-05-06 13:19:07]

The debate on the qualities of science reveals a remarkable blind spot as to where the real problem is about a truly scientific understanding of reality in a complete way. Few if any of the debaters have noticed as yet the essential problems:
The writer seems to place the whole burden on the scientific community and its supposed pressure to avoid popular writing, but we have accumulated a great amount of detail in every field of science. Communicating these details and retaining the interest of general public while doing so, take significantly longer than the science that directly affects everyday life. An additional challenge for scientists and science journalists is to compete for the very small amount of time that people can afford to spend learning about a newly discovered gene or the large hadron collider. People's minds are filled with things like the next blockbuster cell phone to game schedules and TV shows. Even the "Breakfast Club" scientists may not have effectively conveyed the details of their findings as well clearly. This is the same now as it was then. I appreciate your call to action.

I agree partly twice by Richard Patrock, [Comment posted 2011-05-06 12:31:14] A typical academic scientist in the US has many duties including, teaching, doing the research, getting funding to do the research, managing a lab, institutional administration, publishing the science, and anything that comes along. So, is it outreach to educate the public also making it to the list? I don't think so, someone specialized on that should be in charge.

Another chore for scientists? by anonymous poster, [Comment posted 2011-05-06 12:34:11] Thanks for this informative and stimulating posting. I agree that modern professional science doesn't connect very well with contemporary popular culture (and vice versa). Lots of room for improvement. But I question whether this disconnect was any less severe 150 years ago, in the era of amateur "natural philosophy". It's hard to imagine a man more out of step with the popular beliefs of his day than Charles Darwin. We tend to forget how rock-solid was the belief in the literal truth of the Bible, in Darwin's England. It's not a question of professional vs. amateur. It's a question of how well the general populace has been educated in scientific thinking. Today, poorly; back in the day, not at all. Scientific thinking is counter-intuitive; superstition is the natural tendency of the untrained mind. Popular science writing isn't gonna get the job done. The revolution has to be in our education system. Politically, it looks unattainable, but I suppose that's been true of all revolutions.

The devil is in the details by ANIL CASHIKAR, [Comment posted 2011-05-06 11:58:36] Perhaps scientists should try to connect with the real world and stop being so isolated from what actually matters to people. Be more humble and less arrogant, rather than assuming that what you do is the most important thing in the world. Be helpful and give back more to those who pay your wages.

Revolution on Two Fronts by Lundy Pentz, [Comment posted 2011-05-06 10:32:37] The burden of science communication cannot be placed squarely only on scientists. As science has progressed over the past 200 years from the Breakfast Club to modern science, one must not ignore the fact that w
By Hannah Waters

**Vaccine primes T-cells for SIV**

A new vaccine that uses a persistent virus vector controlled SIV in 50 percent of tested monkeys  
[Published 11th May 2011 06:00 PM GMT]

A new vaccine for simian immunodeficiency virus (SIV), a model for HIV, controlled SIV in half of tested rhesus monkeys, research published today (May 11) in *Nature* reports. The vaccine, which employs a viral vector that remains latent throughout the body for a lifetime, appears to keep T-cells active and ready to fight the invading virus.

"This is an absolutely momentous development," said pathologist Peter Barry of University of California Davis who was not involved in the research. "There is still room for optimization, but it's really quite remarkable that they're getting essentially 50 percent control."

Scientists have struggled to develop an effective vaccine against SIV and HIV, in part due to how quickly the viruses spread through the body and evolve to evade immune defenses. Previous vaccines, such as the one tested in the failed STEP trial in 2007, encoded HIV antigens into an adenovirus, but because the vector is short-lived, the memory T-cells generated by the vaccine retreat to the lymph nodes to await another attack. In this position, the T-cells are too slow to respond to an incoming HIV infection, said immunologist Louis Picker of Oregon Health and Science University. By the time they leave the lymph nodes to proliferate and differentiate into effector T-cells, which do the actual fighting, HIV has already spread beyond control. To be effective, he hypothesized, an HIV vaccine should constantly stimulate the body's defenses to attack the virus as soon as it enters the body, when it is the most vulnerable.

To do this, Picker and his colleagues engineered SIV antigens into a cytomegalovirus (CMV), a latent virus that can persist throughout the body asymptotically for long periods. The researchers gave the vaccine to 24 rhesus macaques, then infected them with SIV more than a year later. Thirteen of the monkeys controlled the virus at initial infection, quickly reducing the virus in blood to undetectable levels. Over the following months, the virus reemerged in those animals, but 12 of the 13 monkeys were once again able to fight it back down.

"This pattern of this protection—when the virus went up and came down instead of remaining at baseline—supports their claim that the immunity needs to persist" to effectively control the virus, said Ira Berkower, chief of the laboratory of immunoregulation at the US Food and Drug Administration, who was not involved in the research.

The vaccine does not prevent infection, however, but rather limits viral levels to nearly undetectable levels, added Berkower. As a result, "if [the] immune system should ever be immunosuppressed or attenuated in some fashion, you could get full blown virus."

Furthermore, while CMV's ability to persist in the body may boost the effectiveness of the vaccine, the viral vector could also become a safety concern should a patient's immune system be compromised, said Genoveffa Franchini, a retrovirologist at the Center for Cancer Research at the United States National Institutes of Health who was not involved in the research. It will be "very difficult" to satisfy all the safety requirements of a vaccine that requires giving "a chronic virus for the rest of [one's] life."

Since 50 percent of the US population over 55 has latent CMV already, you "could make a case for testing it in [already infected individuals] to find out if it's immunogenic in people," said Berkower. "But at the end of the day, you'd like to have something safe enough for everybody."

Picker and his team are currently working to engineer a safety-enhanced CMV vector with lower pathogenicity. "To me, it's promising that we can make a safe vector that works and could have benefits to humans," Picker said.

By Harriet L. Robinson

**Opinion: Progress toward an HIV/AIDS vaccine**

*Recent successes and ongoing efforts to develop a successful vaccine*

[Published 11th May 2011 12:56 PM GMT]

A week from today (May 18) marks HIV Vaccine Awareness Day, an occasion designed to salute individuals on the front lines of efforts to develop a preventative vaccine against HIV. The drive to eradicate global AIDS is facing unprecedented challenges, with a report in The New York Times last year describing it as a war we are losing due to financial and technical roadblocks.

Yet tremendous progress is being made towards the development of an effective vaccine. In autumn 2009, a collaborative effort between the Ministry of Health in Thailand, the US Military, and the US National Institute of Allergy and Infectious Disease (NIAID) announced the first encouraging results from an efficacy trial—31 percent prevention of infection in a 16,402 person community-based trial in Thailand. This result achieved significance (p = 0.04) in an analysis that excluded the 7 subjects who were found to have been infected at the time of the first vaccination, demonstrating for the first time that an HIV vaccine can prevent infection.

This trial, the third efficacy trial to be conducted for candidate HIV/AIDS vaccines, was the first to test a product designed to elicit both antibodies and T cells. This vaccine used a recombinant canarypox vaccine to prime immune responses plus protein subunits of the HIV surface protein (termed gp120) to boost immune responses.

Further analysis of the data suggested that protection (prevention of infection) had peaked at 60 percent at 6 months following the fourth and final vaccination, waned to 44 percent 12 months later and to 34 percent by 2 years following the final vaccination (AIDS Vaccine 2010, Atlanta GA, September 28-October 1, 2010)—declines associated with decreasing levels of the antibody responses over time. Thus, this vaccine, if regularly boosted to maintain antibody responses, might have the potential to achieve 60 percent prevention from infection—a credible level of protection for a new vaccine.

Until the Thai trial, many considered the best achievable outcome for an HIV/AIDS vaccine would be to induce immune responses capable of controlling, but not preventing, infection. The data from the Thai trial suggested that prevention from infection is a possibility. Since the Thai trial, complete prevention from infection has been achieved in non-human primate models when repeated rectal or vaginal virus challenges are used to mimic sexual transmission. The repeated-dose challenges are typically administered weekly for 6 to 12 weeks using a dose of virus that infects 30 to 50 percent of unvaccinated animals at each challenge event. This dose is much greater than the amount of HIV in a typical human exposure. Thus there is hope that the results in the non-human primate models will translate into vaccine-induced prevention in humans.

At Geovax Labs Inc., we are working on a combination vaccine in which the first component is a DNA vaccine co-expressing granulocyte-macrophage-colony stimulating factor (GM-CSF) and HIV virus-like particles that prime the immune response and the second component is an attenuated vaccinia virus (MVA) also engineered to express HIV virus-like particles to boost that response. Using prototype vaccines in monkey models, we have been able to demonstrate that this combination is capable of achieving a highly encouraging 70 percent prevention from infection (L. Lai, et al., *Jour Inf Dis*, in press).

When we measured how tightly the vaccine-elicited antibodies bound to the envelope protein of the challenge virus (a measure called the avidity), we found that it correlated with prevention of infection. We are highly encouraged by these results and, in collaboration with the NIAID, are advancing the GM-CSF concept into human clinical trials.

Several other companies are also working toward an AIDS vaccine. Aventis-Pasteur and Global Solutions for Infectious Diseases, which provided the vaccine for the successful Thai trial, are preparing product to test the ability of their vaccine, given with regular boosts, to protect Thai men who have sex with men. Other efforts include those of GlaxoSmithKline, which is testing adjuvants with proteins; the Netherlands-based biopharmaceutical company Crucell, working with Harvard University to develop new adenovirus vector-based vaccines; Pennsylvania-based Inovio, which is developing a vaccine that contains viral DNA plus a cytokine; Maryland-based Profectus, which is developing DNA, protein and vesicular stomatitis virus-vectored vaccines; and Novartis, which is working on adjuvanted protein vaccines as well as viral vectors. The European company Mymetics is developing virosomes displaying gp41 derived proteins as a mucosal vaccine. Aventis-Pasteur, in tandem with Eurovac, a European vaccine consortium, is working on developing additional live poxviral vectors to be used with protein boosts from Novartis.
develop an HIV/AIDS vaccine and look to the future advancements of these efforts, we have cause for optimism. The AIDS vaccine field has generated evidence for the ability of vaccines to prevent HIV infection in humans, and there is hope that the low levels of prevention achieved thus far can be enhanced by regular boosting. The field has also developed new non-human primate models for testing vaccines, enabling researchers to clearly distinguish the ability of prototype simian vaccines to prevent infection. I am confident vaccines will conquer the AIDS pandemic. Tremendous progress has been, and is continuing to be made.

Harriet L. Robinson, PhD, is Chief Scientific Officer at GeoVax Labs and is the developer of the company’s HIV-1 AIDS vaccine technology. She can be reached at hrobinson@geovax.com.

Comment
There is Progress toward an AIDS Vaccine From Another Front
by ROULETTE WM. SMITH, [Comment posted 2011-05-11 23:55:05]
After more than 28 years in attempting to direct attention to a logically-derived indirect approach to vaccines against AIDS (though not HIV per se), I intend to move forward aggressively in demonstrating the reliability, validity and economic feasibility of an inferred approach cited in US Patent Number 7,826,974 B2.

Session B9, oral presentation: Sterling, PREVENT TB: Results of a 12-Dose, Once-Weekly Treatment of Latent Tuberculosis Infection (LTBI)
Research offers simpler, effective treatment option for latent TB infection
Results from one of the largest U.S. government clinical trials on tuberculosis preventive therapy to date suggest that treatment for latent tuberculosis (TB) infection — normally a difficult and lengthy regimen — may soon be easier than ever before in countries with low-to-medium incidence of TB. The trial results showed that a supervised once-weekly regimen of rifapentine and isoniazid taken for three months was just as effective as the standard self-administered nine-month daily regimen of isoniazid, and was completed by more participants.

The multi-country, CDC-sponsored trial tested the effectiveness of this new preventive TB treatment regimen (using currently available anti-TB drugs) among persons with latent TB infection who are at high risk for progression to TB disease. The results were presented today at the American Thoracic Society International Conference in Denver by principal investigator Timothy Sterling, M.D., of Vanderbilt University.

“Although the standard regimen is very effective in treating latent TB infection, ensuring that those who need treatment both begin and complete the lengthy, cumbersome isoniazid regimen is challenging,” said CDC Director Thomas R. Frieden, M.D. “New, simpler ways to prevent TB disease are urgently needed, and this breakthrough represents one of the biggest developments in TB treatment in decades.”

Latent TB infection occurs when a person has TB bacteria in his or her body, but does not have symptoms and cannot transmit the bacteria to others. However, if the bacteria become active, the person will develop TB disease, become sick, and may spread the disease to others. Although not everyone with latent TB infection will develop TB disease, some people, such as those with weakened immune systems, are at higher risk of progression to TB disease.

The new regimen to treat latent TB reduces the doses required for treatment from 270 daily doses to 12 once-weekly doses, making it much easier for patients to take.

In the United States, the number of persons with TB disease is at an all-time low (11,181 total cases were reported in 2010); however, approximately 4 percent of the U.S. population, or 11 million people, are infected with the TB bacterium. TB continues to disproportionately affect racial/ethnic minorities and foreign-born individuals in this country.

“If we are to achieve TB elimination in the United States, we must address the large number of people in this country with latent TB infection,” said Kevin Fenton, M.D., director of CDC’s National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention. “By effectively treating latent TB infection, not only can we reduce the potentially deadly consequences among those individuals, but we can also prevent many others from ever becoming infected.”

One of the largest TB prevention trials to date
The study lasted approximately 10 years and included 8,053 participants over the age of 2 who lived in countries with low or medium TB incidence, with the majority from the United States or Canada. Additional participants were located in Brazil and Spain. Because of a known drug interaction between
some anti-HIV drugs and rifapentine, HIV-infected persons taking antiretrovirals were not eligible for enrollment in the study.

Participants were randomized to receive one of two preventive treatment options – a regimen consisting of three months of once-weekly rifapentine 900 milligrams and isoniazid 900 milligrams given with supervision (that is, directly observed therapy), or the current standard regimen used to treat latent TB infection, consisting of nine months of daily isoniazid 300 milligrams, which was not supervised (that is, self-administered by the participant). Each participant was evaluated for treatment-related adverse events, adherence to treatment, survival, and development of TB disease for a total of 33 months after the date of their enrollment.

The new regimen was found to be safe and as effective as the standard regimen in preventing new cases of TB disease, with very few cases of TB disease developing in either study arm. Seven cases occurred among those receiving the new treatment regimen compared to 15 among those receiving the standard treatment. Additionally, the percentage of participants completing the new, shorter regimen was substantially higher (82 percent) than the percentage completing the standard regimen (69 percent).

**Next steps in implementation**

Given the promise of these results, CDC has already held an expert consultation to review the data and begin working on new guidelines for its use in the United States. Researchers caution that these results are only directly applicable to countries with low-to-medium incidence of TB. Additional studies will likely be needed before this new regimen can be recommended in countries with a high incidence of TB, especially those with high HIV prevalence and where the risk of TB re-infection is greater.

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**Legal Barriers to Wide HIV Testing Now Mostly Gone**


HIV testing laws in most states are now compatible with CDC recommendations to streamline diagnosis of the virus, according to a new report. Five states still have testing laws incompatible with at least one aspect of CDC’s 2006 HIV testing recommendations, down from 16 states in 2009. The data are based on the January 2011 update to the Compendium of State HIV Testing Laws.

In 2006, CDC recommended HIV screening in health care settings for all patients ages 13-64 unless they specifically decline the test. The agency advised that general consent to medical care include the offer of HIV testing—whereas some states required separate, written consent solely for HIV testing—as well as streamlined pre- and post-test counseling.

Since then, 24 states have changed their laws to embrace CDC’s recommendations, according to Sarah Neff, MPH, and Ronald Goldschmidt, MD, of the University of California-San Francisco. As of the January update to the compendium, 46 states and jurisdictions (including District of Columbia) had laws that were compatible with CDC’s HIV testing guidance.

The five states whose HIV testing laws remain incompatible are Maine, New York, Nebraska, Pennsylvania, and Rhode Island, reported Neff and Goldschmidt. Maine requires opt-in testing, in which patients must expressly request an HIV test. Pennsylvania and Rhode Island have counseling requirements that are at odds with CDC recommendations.

Maine and Nebraska both mandate separate HIV testing consent and they, together with New York and Pennsylvania, also require written rather than oral consent. New York does allow oral consent for rapid HIV testing.


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**Ugandan Parliament Fails To Debate Legislation Criminalizing Homosexual Acts**

*Legislation* that criminalizes homosexual acts in Uganda did not make it to the floor of the country’s Parliament on Friday, meaning “the bill is essentially dead, for the moment,” PRI’s "The World" reports (Porter, 5/13).

"Friday's shelving of [Member of Parliament David] Bahati's anti-homosexuality bill is a victory for Uganda's hidden gay community, but it is not the end of the anti-gay legislation," GlobalPost reports, adding that Bahati told the news agency he plans to propose a new bill in the next parliamentary session "to ensure we have a law to stop recruitment and promotion [of homosexuality]" (McConnell, 5/13). The new parliament begins in June, VOA News reports in an article examining violence against gays in Africa (DeCapua, 5/13).
Sanofi Hopes To Launch Dengue Vaccine In 2014

France's Sanofi-Pasteur, the world's largest vaccine maker, said Friday it hopes to introduce a dengue vaccine in 2014 to some high-risk nations, AlertNet reports. The vaccine is in the last stage of clinical testing in Australia, and the company said it hopes to produce 100 million doses of the vaccine annually, according to the news agency.

More than half of the world’s population is at risk of the mosquito-borne disease, and there currently is no cure or vaccine. An estimated 220 million infections occur worldwide each year, and about two million people, mostly children in Asia and Latin America, develop a serious form of the disease called dengue hemorrhagic fever, AlertNet notes (Girardon, 5/13).

An APT(amer) approach to preventing HIV transmission

The HIV epidemic is continuing spread and efforts to develop a vaccine that protects against infection are still showing limited promise. Therefore, researchers are seeking to develop alternative approaches to block HIV transmission. One such strategy is vaginal application of an agent known as a microbicide, which works to kill the virus at the site of entry into the body. A team of researchers, led by Judy Lieberman, at Harvard Medical School, Boston, has now developed a new agent that they hope could be used as the active ingredient in a microbicide to prevent HIV transmission.

HIV infects cells in the body that express the protein CD4. Lieberman and colleagues generated CD4 aptamers (a structured RNA that binds CD4 with high affinity) fused to small inhibitory RNAs targeting the HIV gag or vif genes (which template essential HIV proteins) or the human CCR5 gene (which templates a protein key to HIV entry into cells). These chimeric aptamers were taken up by CD4+ cells, where they knocked down expression of their target genes. More importantly, they inhibited HIV infection of primary CD4+ cells in vitro and of CD4+ cells in polarized human cervicovaginal explants. Furthermore, when applied vaginally to humanized mice they protected against vaginal transmission of HIV. Although additional studies are required to determine how long gene silencing and protection lasts, these data suggest that microbicides containing CD4 aptamers fused to defined small inhibitory RNAs could provide a new tool in the fight against HIV/AIDS.

Title: Inhibition of HIV transmission in human cervicovaginal explants and humanized mice using CD4 aptamer-siRNA chimeras

Duke-NUS researchers identify new cell that attacks dengue virus

Durham, N.C., and Singapore – Mast cells, which can help the body respond to bacteria and pathogens, also apparently sound the alarm around viruses delivered by a mosquito bite, according to researchers at Duke-NUS Graduate Medical School in Singapore.

"It appears the mast cells are activated and call immune system cells to the skin where they clear infection, which limits the spread of infection in the host," said lead researcher Ashley St. John, a Research Fellow with Duke-NUS in the Program in Emerging Infectious Diseases, and the Duke Department of Pathology in Durham, N.C.

Studying dengue virus in mice, the research team found that mast cells can sense and recognize viruses, and in turn release signaling chemicals to create an immune response.

The scientists chose to study dengue virus, which is common in Singapore, because mosquitoes inject the virus through the skin, and skin is rich in mast cells.

They found that mice lacking mast cells had more of the virus in their lymph nodes and increased infection after measured injection with a small dose of dengue virus, compared to mice with normal levels of mast cells. The mast cells produce chemokines, which in turn help to bring some special killer cells into the infected skin to fight and contain the virus.

"It was an important discovery for the field to learn that mast cells could be activated by pathogens like bacteria or parasites," St. John said. "We were excited to learn that mast cells also respond to and promote the clearance of a viral infection."

"The finding is important because to date there are no vaccines or effective therapies for dengue fever," said senior author Soman Abraham, Ph.D., Professor of Pathology and mast-cell expert, also in the Program In Emerging Infectious Diseases.

St. John said that the finding opens new paths to explore. Because mast cells are involved in airway reactions, as during an asthma attack, this new finding might also help scientists study viral infection in the lungs, airways and sinuses.
She noted that other mosquito-borne viruses could also be studied in terms of mast-cell response, like the West Nile virus.

"Now that we know mast cells can recognize viruses, we can better understand how that infection process begins," Abraham said. "Knowing the important role of mast cells in viral infections could help find ways to prevent these infections, perhaps in the form of vaccines." Because mast cells can be deliberately activated and also shut down with small molecules, different approaches can be studied, he said.

May 16, 2011

**Sandia National Laboratories unlocks secrets of plague with stunning new imaging techniques**

ALBUQUERQUE, N.M. – Researchers at Sandia National Laboratories have developed a super-resolution microscopy technique that is answering long-held questions about exactly how and why a cell’s defenses fail against some invaders, such as plague, while successfully fending off others like E.coli. The approach is revealing never-before-seen detail of the cell membrane, which could open doors to new diagnostic, prevention and treatment techniques.

“We’re trying to do molecular biology with a microscope, but in order to do that, we must be able to look at things on a molecular scale,” says Jesse Aaron, postdoctoral appointee at Sandia Labs.

The cell membrane is a bustling hub of activity on a miniscule scale. While providing structure and housing the cell’s interior, the membrane regulates movement of materials in and out of the cell, controls adhesion to other objects and coordinates the cell’s communications and subsequent actions through signaling. Receptor proteins on the surface of immune cells, known as toll-like receptors (TLRs), are tasked with recognizing intruders, or antigens. The TLR4 member of this receptor family responds to certain types of bacteria by detecting lipopolysaccharides (LPS) present on their surface. TLR4 proteins then alert the cell and activate an immune response.

Using imaging techniques they developed, Sandia researchers Aaron, Jeri Timlin and Bryan Carson discovered that TLR4 proteins cluster in the membrane when confronted with LPS derived from E.coli, which increases cell signaling and response. Interestingly, LPS derived from the bacteria that cause plague, Yersinia pestis, do not cause the same effects. This could explain why some pathogens are able to thwart the human immune system.

The plague studies marked the first time such small events have been imaged and compared, the Sandia researchers said. Previously, even the most sophisticated optical microscopes could not image the cell surface with enough spatial resolution to see the earliest binding events, due to the diffraction barrier, which limits what can be resolved using visible light.

“With more traditional visualization methods, you can’t see the level of detail you need. It’s important to look at not only what’s present, but also when and where it’s present in the cell,” Timlin said.

The technique used by Timlin and Aaron builds on superresolution capabilities developed in recent years, but goes another step by adding dual-color capabilities to the relatively new stochastic optical reconstruction microscopy, or STORM. The combination enables the Sandia team to get a more complete picture by simultaneously imaging LPS and TLR4 receptors on the membrane.

“Current light microscopy capabilities are akin to looking out the window of an airplane and seeing the irrigation circles. You know that plants are there, but you can’t tell what kinds of plants they are or what shape the leaves are,” said Carson, a Sandia immunologist who was an integral part of the project.
“But with this technology, it’s like zooming in and seeing the leaves and the structure of the plants. That buys you a lot in terms of understanding what’s happening within a cell and specifically how the proteins involved interact.”

In 2009, the National Institutes of Health awarded Timlin a five-year, $300,000-a-year innovation grant. Next on the team’s agenda is developing the capability to image live cells in real time using spectral Stimulated Emission Depletion, or STED. “We’re working toward using a version of superresolution that’s much more live-cell friendly, and extending that in terms of what colors are available to do multiple colors, while maintaining the live-cell friendliness. I see this as a beginning of a long development in this type of imaging technology,” Timlin said.

Potential applications likely will expand as the technology reveals previously unattainable details of cell signaling. Eventually, the Sandia team would like to be able to visualize protein/protein interactions.

“Every biological process that goes on in your body is somehow controlled by proteins forming complexes with other proteins or complexes in the membrane, so this would give you this ability to look, with high spatial resolution and multiplexed color capabilities, at four or more things in a living cell, which can’t be done very easily right now. It can be done in pieces, but we want to see the whole biological process,” Timlin said.

The technology has exciting potential in immunology and drug discovery. Improved imaging could show the mechanisms viruses use to invade cells, which might lead to drugs that would block entry. “We’re hoping to do something like label the viral particles and watch them in real time, or as close as we can to real time, in the internalization process,” Carson said. “With the superresolution technique, we can actually watch them move through the membrane and see if there are other structures being recruited by the virus to the site of internalization.”

Sandia originally developed the technology in support of its biological national security programs, but the team wants to expand the technology into other areas such as biofuels to better understand where and when different pigments are located on the membrane of oil-producing algae. This would provide valuable insight into their photosynthesis functions, which could lead to more efficient biofuel production.

“A lot of this work is in its early stages, but we’re encouraged by what we’re seeing and excited about its future potential,” Aaron said.

**Stopping HIV Transmission With a Molecular Barrier?**

ScienceDaily (May 16, 2011) — Using a technique that silences genes promoting infection, researchers have developed a novel, topically-applied molecular microbicide capable of preventing HIV transmission. The microbicide is predicted to have long-lasting effects in mice, opening the door to developing an intravaginal microbicide that could protect women against HIV infection potentially for weeks at a time and bolster public health efforts to halt the spread of HIV/AIDS.

The study, led by Lee Adam Wheeler and Judy Lieberman, MD, PhD, of the Immune Disease Institute and the Program in Cellular and Molecular Medicine at Children’s Hospital Boston, was published online on May 16 in the *Journal of Clinical Investigation*.

The microbicide takes advantage of a molecular phenomenon called RNA interference (RNAi), in which small pieces of RNA called small interfering RNAs (siRNAs) silence the expression of individual genes with complementary sequences. Originally observed in plants, RNAi was found to be active in mammals only a decade ago, but it is already the focus of many clinical investigations.

Lieberman and Wheeler chose to investigate RNAi’s potential to provide a molecular barrier against HIV transmission based on earlier work in her laboratory showing that the phenomenon could be harnessed to prevent herpes simplex virus (HSV) transmission, and also on recent advances in understanding how HIV penetrates the body. “The current model of HIV transmission holds that the virus is localized to the genital tract for about a week, which could provide a window of opportunity to intervene and prevent the infection from establishing itself throughout the body,” said Lieberman. “And last year it was shown that it is possible to prevent HIV transmission, at least to some extent, with a topical vaginal agent using an antiviral drug, thus providing proof-of-principle that a topical strategy could interfere with virus transmission.”

In the current study, the researchers used siRNAs that turned off two viral genes and that of one of HIV’s two host co-receptors, CCR5. HIV uses CCR5, found on immune cells called T cells and macrophages, to gain entry into an uninfected person’s immune cells and establish a foothold within the body. Individuals harboring mutations that deactivate CCR5 are resistant to infection with HIV.
To ensure that the siRNAs would be delivered only to the immune cells targeted by HIV, the research team linked the siRNAs to an aptamer—a second piece of RNA designed to attach to a specific molecule—that binds to HIV's main receptor, CD4, to create CD4 aptamer-siRNA chimeras (CD4-AsiCs).

"By using CD4 as a binding site but knocking down CCR5, we get specificity for the cells targeted by HIV but avoid the risk of interfering with the overall immune response," Lieberman noted.

When tested in vitro using cell lines and blood cells, the CD4-AsiCs bound only to immune cells displaying CD4 on their surface; turned off expression in those cells of the three targeted genes; and prevented HIV replication. In addition, CD4-AsiCs successfully penetrated cultured human cervicovaginal tissues to reach immune cells deep within the tissue layers, silence target gene expression, and prevent HIV infection of the cultures.

To test the effectiveness of this system in vivo, the study team applied CD4-AsiCs topically within the vaginal canal of female mice with humanized immune systems, and then exposed those mice intravaginally to HIV so as to mimic sexual transmission of the virus. As in the in vitro model, the CD4-AsiCs were able to penetrate through the vaginal walls of these mice to the immune cells within the tissues, deliver the siRNAs to cells displaying CD4, and turn off the expression of the targeted genes. Over the following 12 weeks, none of the mice treated with the siRNAs showed any biological signs of HIV infection, while all of the control mice progressed to full-blown HIV infection.

Lieberman thinks that the RNAi-based microbicide's specificity and duration of action make it attractive for further pharmaceutical development. "The problem with most topical methods for preventing sexual transmission of disease is that you have to use them just before having sex, and compliance is a huge issue," she said. "But our laboratory results show that we can knock down CCR5 expression potentially for weeks, suggesting that we could create a stable viral-resistant state where one would only have to apply the agent every couple of weeks."

According to Wheeler, the method's modularity suggests that its promise is not limited to HIV. "You could basically switch in or out any kind of siRNA or aptamer for any binding target to knock down any gene you would want, be it host or viral." Lieberman added, "Conceivably, one could include siRNAs against multiple viral agents in a cocktail to gain protection from multiple sexually transmitted diseases, including HSV and human papilloma virus."

Journal Reference:

By Cristina Luiggi

**Engineered proteins for fighting flu**

In a feat of computational biology, researchers design novel proteins capable of neutralizing a key influenza protein

[Published 12th May 2011 06:37 PM GMT]

Computational biologists designed and produced two novel proteins that strongly bind to a crucial flu protein that enables the virus to enter cells. The new creations, built with the help of more than 200,000 personal computers around the world, may one day serve as effective antiviral therapies, according to a study published today (May 12) in Science.
“This study is remarkable,” said John Karanicolas, a University of Kansas computational biologist who did not contribute to the research. "This is a method which in the long run may absolutely be a useful complement to antibody technology both for diagnostics and therapeutics.”

To design proteins to interact with a desired target, such as a pathogen's protein, researchers can scan extensive libraries of protein structures in search of a few that roughly complement the target molecule, then tweak those structures slightly to produce a tighter fit. Alternatively, they can introduce the pathogen to an animal to coerce its immune system to respond to the target, and then select from the antibodies that are generated.

While the former approach grants researchers control over where and how the designed proteins will bind to the target, they may not bind as strongly to the target. The latter, more "natural" approach, on the other hand, may yield antibodies that have a high affinity for the target molecule, but researchers have little control over the dynamics of binding.

But with quickly-evolving target molecules such as the influenza virus's surface protein, hemagglutinin, which has a large area that is constantly mutating and changing to evade antibody binding, even antibodies that bind well are often rendered obsolete in time.

To tackle this challenge, computational biologist David Baker of the University of Washington and his colleagues decided to focus on a region of hemagglutinin that tends to be quite stable and is conserved among many influenza strains. Antibodies that bind to this region have been shown to prevent the virus from fusing its membrane with a host cell's and cause infection.

To target this region of the protein, the researchers had to work on the problem in reverse, first searching for "nooks and crannies" in that region where a protein would be able to take hold, Baker explained, and then identifying strings of amino acids that could fit in those spaces and act as hooks.

Once they created an entire library of these hooks, they searched proteins with known structures for those that would roughly fit the conformation of hemagglutinin and serve as the main protein bodies to hold the hooks.

The researchers then modified the orientation and sequence of these scaffold proteins to hold the hooks in positions so that they could interact with hemagglutinin. For this critical, time-consuming step, the researchers reached out to the public for help in solving and optimizing the 3D structures of the proteins. Around 250,000 volunteers downloaded free software developed by Baker's lab called Rosetta@home, which allowed their personal computers at home to contribute computing power for the complex calculations.

"The design approach was really extraordinary," said Tanja Kortemme, a computational biologist at University of California, San Francisco, who did not participate in the study. "They turned the problem around by first finding the amino acid side chains that formed the interactions that they wanted, and then finding a backbone that could display those side chains."

All in all, the researchers came up with around 80 novel proteins. When expressed on the membranes of yeast, however, only two were able to bind to hemagglutinin, and the binding strength had to be further improved by slightly tinkering with the amino acid sequences.
“The success rate is still very low,” Baker said. But comparing a crystal structure of one of the two designs that bound to hemagglutinin with the initial computational model from which the protein was designed, he found they were essentially superimposable, an extremely rare accomplishment in de novo protein design. Thus, although the model still needs improvement, it was able to successfully predict an interaction between two proteins.

The fact that the researchers produced two very different designs that worked for the same target is also cause for great optimism, added Karanicolas, who did his postdoc in Baker’s lab at the University of Washington. "The real strength of this method is that it allows control of the design in the very early stages."


By Robert Michael Stroud

**An Insoluble Problem?**

The challenges of crystallizing membrane proteins—and how they’re being overcome

Computer artwork of a G protein-coupled receptor in the lipid bilayer of a plasma membrane Medi-Mation Ltd / Photo Researchers

Membrane proteins represent only a handful of the total number of protein structures defined to date. Yet these proteins, which represent nearly 40 percent of all known proteins, including receptors, channels, and signaling molecules, are essential for cell communication and their malfunctions are implicated in many diseases. Structure-based design is one powerful way of developing drugs tuned to the precise actions and minimal side effects required for effective treatments. X-ray crystallography—still the only general method for solving the atomic structures of proteins of any size—has been hampered by the extreme difficulty of preparing and crystallizing pure membrane proteins.

The problem is a practical one: hydrophilic proteins, such as those in the cytoplasm, can form crystals in solution relatively easily, but membrane proteins also have hydrophobic parts that buoy the protein in the lipid layer. To maintain their shape, these lipid-loving domains must be surrounded by components that resemble the natural membrane—a requirement that makes it difficult to grow well-diffracting crystals. However, an array of technical advances over the last 2 years has advanced our ability to determine these structures.
Extracting and stabilizing
Advances are the result of developments at multiple steps in the crystallization process. One example comes from Raymond Stevens and colleagues at the Scripps Research Institute who discovered that lipids were essential for determining the structure of a G protein-coupled receptor (GPCR) that responds to adrenaline. When Stevens tried to crystallize his GPCR, he found that cholesterol molecules were necessary for crystal formation, and from the structure, showed that cholesterol also acted as glue between the dimeric receptor molecules. This gave a structural explanation for the observation that cholesterol in the membrane is essential for the dimerization, and hence the signaling function, of this receptor.

The choice of detergent used to isolate membrane proteins can also have a profound effect on their ability to crystallize. Classical detergents, such as beta-octyl glucoside, create relatively large lipid globules, called micelles, which contain a single layer of phospholipids with their single-chain tails facing inward. Large micelles increase the ratio of lipid to protein, making it difficult to pack the protein to a density sufficient for crystal formation. Stevens collaborated with chemists to design new detergents, such as the cholate-based amphiphiles, that create smaller micelles, allowing the protein molecules to pack more closely and form better crystals. A third factor that can improve crystallization is the origin of the protein. The volume and quality of proteins produced depends on the organism, cell type, promoter, and vector used to generate them. However, there is no way of knowing in advance which species or expression method is going to yield a well-behaved protein. Because many membrane proteins are expressed by multiple species, homologous genes should be tested and screened to identify proteins that are most amenable to crystallization. Researchers can now use high-throughput methods to screen large numbers of expression and purification conditions, which helps to speed the process.

A remarkable example of such optimization comes from Rod MacKinnon’s lab at The Rockefeller University. Interested in the mechanism of a CLC chloride transporter protein, they tried to improve the data they obtained from their crystal by replacing a naturally occurring amino acid with a methionine at each of 30 sites in the protein. They then tagged the methionines with the heavy element selenium, which helped them confirm the atomic structure of the protein with better precision.

Redesigning the protein
Chopping off the termini of proteins is a trick long-used to make soluble cytosolic proteins more amenable to crystallization. Similarly, removing the hydrophilic and flexible ends of a membrane protein can improve crystal formation. By excising flexible regions of human aquaporin 4, a water channel implicated in the ALS-like autoimmune disease neuromyelitis optica, we obtained a high-resolution structure. Another approach is to insert mutations that alter the protein sequence in a manner that stabilizes one particular conformation, and screen to find those that might rigidify otherwise flexible regions.

More drastic engineering—whole gene redesign—can make it possible to solve structures of proteins that were not amenable to study by other means. Some amino acids have multiple codons—the triplets of nucleotides that make up the genetic code—and different species prefer to use different equivalent codons to make the same protein, an effect known as codon bias. Because codon bias affects translation efficiency, taking a gene from one organism and expressing it in a different one can improve protein production. We recently engineered a *Plasmodium falciparum* aquaporin gene to express in the plasma membrane fraction of *Escherichia coli*. But we altered the *Plasmodium* gene sequence to use the codons favored by *E. coli*, a process known as codon optimization. Although the DNA sequence changes, the protein sequence remains the same.

The dramatic technical progress of the last few years has lent new energy to the prospects for determining structures of membrane proteins and how they function. We can now begin to approach the mechanisms of transmembrane processes implicated in a variety of illnesses, such as cancer, diabetes, schizophrenia, and depression, where signaling defects in membrane proteins have previously been difficult to study at the level of atomic structures.

Robert Michael Stroud is at the University of California, San Francisco.

References:
By Hannah Waters

The dark matter of disease

Scientists are beginning to unravel how non-coding DNA works across long distances of the genome to influence disease

[Published 25th April 2011 04:56 PM GMT]

In the early 2000s, geneticist Len Pennacchio was at the Lawrence Berkeley National Laboratory in California studying coronary artery disease (CAD) and was faced with a conundrum: Despite the fact that CAD was a known heritable disorder, he and his colleagues could not identify any gene that significantly contributed to CAD risk. "It's the number one killer in Western society, yet the genetic explanations have largely remained elusive," he said.

But the completion of the Human Genome Project and the release of the first draft genome of Homo sapiens over a decade ago revealed a vast expanse of DNA that scientists hadn't yet begun searching for disease-related genes—non-coding DNA, which is not transcribed into RNA or translated into a protein product. "The main surprise from the project is that only one percent of the genome is coding," said Pennacchio, now the head of the Joint Genome Institute's Genomics Technologies Departments—a miniscule amount compared to the 88 percent and 24 percent of the E. coli and C. elegans genomes, respectively (1). The other 99 percent, often dubbed "junk DNA" or the "dark matter" of the genome, hadn't been well characterized, though many scientists suspected it may play a role in gene regulation and disease. "The project basically opened the whole field to ask the question: What is the function that lies in non-coding DNA?" Pennacchio said.

Scanning the genomes of over 23,000 people, some of whom had severe, early-onset CAD, Pennacchio and his colleagues identified a genetic pattern on the 9p21 region of chromosome 9 where few coding genes were found—appropriately dubbed a gene desert—that increased CAD risk by 30-40 percent in homozygous individuals (2). "It was just fascinating," Pennacchio reflected. "It's a pretty strong link and independent of anything that we knew caused heart disease before." But it was just a correlation, he added. Unraveling the function of this sequence would take a new bag of tricks.

In February, Kelly Frazer and Geoff Rosenfeld, genomic scientists at the University of California, San Diego, and cardiologist and geneticist Eric Topol of Scripps Genomic Medicine connected this 9p21 region to inflammatory signaling in heart cells (3). The region of non-coding DNA that conferred the increased risk of disease was unable to properly bind the transcription factor STAT1, an event which normally regulates the expression of several genes implicated in many types of cancer. The binding appeared to be influenced by cytokines, such as those produced during inflammation of the artery walls in CAD patients, suggesting that the 9p21 region may play a role in the progression of the disease.

In addition to furthering scientists' understanding of CAD, the finding adds to a growing body of literature that links non-coding DNA with changes in expression patterns of known disease genes. Over the past few years, a number of studies have identified genes whose expression correlates with specific non-coding sequences, suggesting that the so-called junk DNA acts to regulate the rate and amount of transcription of other sections of the genome.

"Disease often has to do with producing the right amount of protein at the right place at the right time," said Aravinda Chakravarti, a molecular geneticist at John Hopkins Medicine, whose 2005 research identified a non-coding sequence associated with risk of Hirschsprung disease, a colon disorder with nearly 100 percent heritability (4). In addition to mutations that alter the function of disease-related proteins, "changing the amount of a protein will also create disease."

A variant of a non-coding DNA region on chromosome 8, for example, increases the risk of prostate and colorectal cancers. In 2009, scientists found that the high-risk allele disrupts the binding site for a transcription factor, affecting Wnt signaling, a major pathway in colorectal cancer pathogenesis, and upregulating the expression of the proto-oncogene MYC (5, 6, 7). Similarly, a non-coding region on chromosome 7 was found to regulate the expression of the protein sonic hedgehog (Shh) in the developing limb bud. When the non-coding sequence is mutated, Shh is expressed in abnormal parts of the mouse embryo, resulting in polydactyly, or the growth of extra fingers and toes (8). When this sequence is

completely knocked out, "you lose sonic expression and all limb development," said developmental geneticist Laura Lettice of the UK's Medical Research Council Human Genetics Unit.

But the functions of many non-coding DNA regions associated with disease risk remain unknown. Because non-coding DNA has no RNA or protein product, "it's very hard to think about what are the biological reasons for these associations [with disease]," said Frazer. "It takes more energy, guesswork and intuition" to figure out its function.

"The real question is what does it affect? Which gene?" said Chakravarti. Fortunately, the advent of new technologies, such as chromatin conformation capture (3C), which can help examine how distant parts of the genome interact (9), and high-throughput sequencing coupled with chromatin immunoprecipitation to map histone marks, is making it easier for researchers to answer that question. "Without those types of technological breakthroughs to figure out how to string these things together, it couldn't have been done," said Frazer.

There is one lingering mystery, however—the physical mechanism by which non-coding DNA effects such the changes it does. Current thought holds that transcription factors bind sites embedded in these non-coding regions, initiating a conformational change in chromatin structure. The result is the formation of loops in the DNA, which bring distant points on a chromosome—separated by up to a million base pairs or more—into close proximity, where the non-coding region then engages a gene promoter to activate or inhibit transcription.

"You have to assume that these elements interact with the promoter somehow, and therefore the assumption is that they form loops," said Lettice. "But it's kind of a wee bit hand-wave-y."

Still, scientists in the field are optimistic. "We have not only the genome sequences and the tools, but importantly, we have the perspective of how we go about looking at these problems," said Chakravarti. "We will eventually understand what [these non-coding sequences] are, what they do, what their mutations are, and how they are associated with disease."

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New regimen prevents TB in 12 weekly doses
Keith Alcorn
Published: 17 May 2011

A large trial has shown that a 12-week course of combination treatment for latent tuberculosis is just as effective as a 9-month course of isoniazid in countries with a low to moderate burden of TB, with the additional advantage that the new regimen can be dosed once a week.

The findings, from the Prevent TB study, were presented this week at the American Thoracic Society’s International Conference in Denver.

However, the applicability of the findings for people with HIV and for settings with a high burden of TB is unclear, and more research will be needed.

Latent tuberculosis (TB) is an infection with TB that has been contained by the immune system, does not cause symptoms and cannot be passed on to other people. Latent TB may develop into active TB if the immune system weakens due to malnutrition or HIV infection, for example.

Preventive treatment with a six to nine-month course of the antibiotic isoniazid reduces the risk of developing active TB by between 30 and 60%, but the six to nine month course of daily isoniazid may be difficult for patients to take.

As a result there has been interest in determining whether it is possible to shorten the course of TB preventive treatment.

The Prevent TB trial was designed more than ten years ago, to compare:
12 weeks of treatment with a once-weekly regimen that combined isoniazid (900mg tablet) with a new anti-TB drug rifapentine (900mg injectable), given as directly-observed treatment.

Standard TB preventive TB treatment with nine months of self-administered isoniazid (300mg once daily), the recommended preventive regimen in the United States.

The trial recruited 8,053 participants in the United States, Canada, Brazil and Spain, but excluded participants with HIV infection due to drug interactions between rifapentine and HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors.

Participants were randomised to the experimental regimen or to standard treatment, and followed for 33 months after enrolment to assess the effect on development of active TB and survival, as well as adherence and side-effects.

The new regimen was associated with fewer cases of active TB (7 versus 15 in the standard treatment arm) and better adherence (82% vs 69% completed the course of treatment).

“Although the standard regimen is very effective in treating latent TB infection, ensuring that those who need treatment both begin and complete the lengthy, cumbersome isoniazid regimen is challenging,” said CDC Director Thomas R. Frieden, M.D. “New, simpler ways to prevent TB disease are urgently needed, and this breakthrough represents one of the biggest developments in TB treatment in decades.”

In the light of these results, new US guidelines on TB preventive treatment are expected before the end of the year.

Further research will be needed in countries with a high burden of TB, and in people with HIV. The Tuberculosis Trials Consortium is currently conducting a trial of the isoniazid/rifapentine regimen in people with HIV infection in 7,700 persons.

Reference

Further cuts in drug prices make tenofovir more affordable for low-income countries
Keith Alcorn
Published: 17 May 2011

UNITAID, the international drug purchase fund, and the Clinton Health Access Initiative have announced further price reductions for key antiretroviral drug regimens, including a 14% reduction in the price of tenofovir-based triple combination therapy, to $159 a year.

The reduced prices will be available to over 70 low- and middle-income countries that form part of the CHAI Procurement Consortium, and have been negotiated with a range of generic drug manufacturers.

In part, prices have been pushed lower because of collaboration between pharmaceutical chemists employed by CHAI and generic drug manufacturers, designed to identify ways in which some drugs can be made more cheaply. This work was funded by the United Kingdom government’s Department for International Development.

Reductions in the cost of raw materials has also helped; identifying a new supplier for a key ingredient of tenofovir knocked $15 off the annual cost of tenofovir.

However, it is the prospect of larger guaranteed orders that has galvanised most manufacturers to offer lower prices for new drugs.

World Health Organization guidelines, updated in late 2009, now recommend that wherever possible, people with HIV should start treatment with a tenofovir-based three-drug combination. If that is too expensive, national treatment programmes should use AZT-based combinations, which are less toxic than the d4T-based combinations widely used in the early years of treatment scale-up.

The main price reductions include:

- A reduction in the price of tenofovir-based first-line treatment to $159 a year, down from $400 in 2008, and down 14% in the last year;
- A reduction in the price of a protease inhibitor-based second-line treatment regimen, to $410 a year.

CHAI said that it expects the cost of tenofovir-based treatment to fall below the cost of twice-daily AZT-based treatment within the next few years as demand grows. It projects that demand for tenofovir-based treatment will grow from one million patients in 2010 (18% of the first-line market) to 4.2 million in 2013 (53% of the first-line market).

The World Health Organization recommends that second-line antiretroviral treatment should be protease inhibitor-based, using either atazanavir or lopinavir boosted with ritonavir.
The partners also announced that a co-packaged combination of atazanavir, heat-stable ritonavir, tenofovir and 3TC will soon be available as second-line treatment, subject to approval by the US Food and Drug Administration and the World Health Organization, at a price of $395 a year.

In comparison lopinavir, coformulated with ritonavir, will be available at a generic price of $399 a year without tenofovir and 3TC.

CHAI said it anticipated a rapid switch to atazanavir when the new price becomes available, and further significant reductions in cost as demand grows. (See full price list here).

Switches in drug regimens that drive costs lower will also have the effect of freeing up money to treat new patients. The partners estimate that price reductions could enable an extra 500,000 people to be treated, although this figure assumes that countries would have switched to new drugs without the incentive of price reductions.

However, even without any new enrolment of patients on treatment, the UK Department for International Development estimates that the effort to drive down prices by UNITAID and CHAI will result in savings of $600 million over the next three years when compared with 2008 prices. If treatment scale-up continues at the same pace as over the past three years, the scale of savings could reach $1 billion by 2014.

Apparent Immunity Gene ‘Cures’ Bay Area Man Of AIDS

May 16, 2011 12:25 PM
SAN FRANCISCO (CBS 5) — A 45-year-old man now living in the Bay Area may be the first person ever cured of the deadly disease AIDS, the result of the discovery of an apparent HIV immunity gene.

Timothy Ray Brown tested positive for HIV back in 1995, but has now entered scientific journals as the first man in world history to have that HIV virus completely eliminated from his body in what doctors call a “functional cure.”

Brown was living in Berlin, Germany back in 2007, dealing with HIV and leukemia, when scientists there gave him a bone marrow stem cell transplant that had astounding results.

“I quit taking my HIV medication the day that I got the transplant and haven’t had to take any since,” said Brown, who has been dubbed “The Berlin Patient” by the medical community.

Brown’s amazing progress continues to be monitored by doctors at San Francisco General Hospital and at the University of California at San Francisco medical center.

“I’m cured of HIV. I had HIV but I don’t anymore,” he said, using words that many in the scientific community are cautiously clinging to.

Scientists said Brown received stem cells from a donor who was immune to HIV. In fact, about one percent of Caucasians are immune to HIV. Some researchers think the immunity gene goes back to the Great Plague: people who survived the plague passed their immunity down and their heirs have it today.

UCSF’s Dr. Jay Levy, who co-discovered the HIV virus and is one of the most respected AIDS researchers in the world, said this case opens the door to the field of “cure research,” which is now gaining more attention.

“If you’re able to take the white cells from someone and manipulate them so they’re no longer infected, or infectable, no longer infectable by HIV, and those white cells become the whole immune system of that individual, you’ve got essentially a functional cure,” he explained.

UCSF’s Dr. Paul Volberding, another pioneering AIDS expert who has studied the disease for all of its 30 years cautioned that while “the Berlin Patient is a fascinating story, it’s not one that can be generalized.”

Both doctors stressed that Brown’s radical procedure may not be applicable to many other people with HIV, because of the difficulty in doing stem cell transplants, and finding the right donor.

“You don’t want to go out and get a bone marrow transplant because transplants themselves carry a real risk of mortality,” Volberding said.

He explained that scientists also still have many unanswered questions involving the success of Brown’s treatment.

“One element of his treatment, and we don’t know which, allowed apparently the virus to be purged from his body,” he observed. “So it’s going to be an interesting, I think productive area to study.”

Volberding continued, “Knock on wood, (Brown) hasn’t had any recurrence now for several years of the virus, and that hasn’t happened before in our experience.”

As a result, at the San Francisco AIDS Foundation some are now using the word “cure” after so many avoided it for decades.
“You sort of felt like you couldn’t say ‘cure’ for a number of years. Scientists and clinicians and people with HIV alike felt that was a promise that was never going to be realized and it was dangerous to direct a lot of energy toward it,” said Dr. Judy Auerbach. “And now things have shifted.”

The California Institute of Regenerative Medicine is currently funding stem cell research in the Bay Area based on Brown’s case in the hopes of replicating his success for broader populations of people with HIV.

The institute said it plans to begin clinical trials next year.

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Three Reasons That Big HIV Study May Be Less Important Than It Seems

May 13 2011 — 1:33 pm

Yesterday, a study financed by the U.S. government showed that treating people with HIV as soon as they test positive keeps them from transmitting the virus to their sexual partners almost all the time. But will the study have a big effect in the real world?

Researchers already suspected early treatment could prevent transmission, but this clinical trial proves it is true. (See Mark Schoofs’ definitive account in the WSJ.) The ability to answer a specific question (“does giving patients HIV-fighting drugs early prevent transmission?”) is exactly what makes placebo-controlled clinical trials so powerful. And this is big news – the New York Times put it on this morning’s front page. My colleague David Whelan asks if this means we could get rid of HIV entirely, as we might with a very effective vaccine.

I’m afraid the answer to David’s question is no. I’m not sure that this study is going to have the impact that you’d expect reading the breathless coverage of this study, which researchers refer to as HPTN 052. Here are the reasons for my skepticism.

(1) The stock price of Gilead Sciences, the leading maker of HIV drugs, barely budged yesterday. Wall Street is usually pretty good at sussing out when a medicine’s use is about to expand dramatically. That’s because in the U.S. and Europe, treatment already has expanded. “This is mainly an issue for developing countries where treatment has been more restricted,” says Geoffrey Porges, the biotechnology analyst at Sanford C. Bernstein. “Most public health officials in this country think the case has already been made for treating patients as soon as they are diagnosed here. In the US ‘test and treat’ has been the emerging standard for several years and there are probably only 100,000 patients left who aren’t treated with higher CD4 counts and lower viral loads. Those patients are gradually entering the treated pool already. So maybe it steps up the patient volume growth rate by 2-3 percentage points in the US and Europe, but not much more.”

(2) This study won’t make people who aren’t being treated – either because they don’t want treatment or can’t afford it, more likely to get treated. “A significant number will not be prepared or have the resources to afford medications or they will have barriers (like using drugs) that might interfere with success,” writes Carl Fichtenbaum, a researcher at the University of Cincinnati, via email. “A good idea in principle, but reality is always much messier.”

(3) Reality will be particularly messy in the developing world, where this should have the biggest impact. It’s already hard to get HIV drug cocktails to people there, as Schoofs notes. More data don’t change that. And in places like Africa, many patients aren’t getting the newer drugs, like Gilead’s entrants or Merck’s Isentress, that have milder side effects or better dosing regimens.

Of course, this study does give us more reason to try to get these medicines to those patients. You can’t argue, medically, that more treatment wouldn’t be a good thing. I’m including the below public service announcement as a reminder of why getting HIV drugs to people who need them is so important.

UGANDA: MP to persevere with anti-homosexuality bill

There has been intense local and international pressure against the bills

KAMPALA, 17 May 2011 (PlusNews)—Uganda’s Anti-Homosexuality Bill and HIV Prevention and Control Bill are likely to be carried over to the new session of parliament, despite international and local pressure.

David Bahati, the Member of Parliament who introduced the Anti-Homosexuality Bill (2009), said he fully intended to re-introduce the bill into the next session. The new parliament was sworn in on 16 May.

"The closure of this parliament is just pressing on the pause button," he said. "I'm committed to the fight against behaviour and promotion of behaviour that is going to destroy the future of our children."
Men who have sex with men (MSM) are considered by the Uganda AIDS Commission to be a “most at-risk population”, but because homosexual acts are illegal, there are no policies or services targeting HIV interventions towards them. AIDS activists say the bill would only drive an already stigmatized population further underground, leaving them even more vulnerable to HIV.

MSM are often referred to as a “bridging” population for HIV to the general population, given that many also have sex with women. According to a 2010 survey of 303 MSM in the capital Kampala by the US Centres for Disease Control, 78 percent had had sex with women while 31 percent had been married. The study also found HIV prevalence among participants was 13.7 percent, significantly higher than the city’s average rate of 8.5 percent; knowledge of the risks of HIV was also low.

Amendments
Following consultations with various stakeholders, including the government, civil society and the clergy, the Committee of Parliamentary and Legal Affairs has adopted a number of amendments to the original bill, including the removal of provisions criminalizing “attempted” homosexuality and those requiring anyone who knows of homosexual conduct to report it to the police within 24 hours.

However, according to Human Rights Watch, despite Bahati and other supporters of the bill agreeing to the deletion of the bill’s “death penalty clause”, the parliamentary committee retained the death penalty for those accused of “aggravated homosexuality”, by suggesting it be redefined as “aggravated defilement”, which is also punishable by death.

The committee further recommended the creation of the new crime of conducting a marriage ceremony between persons of the same sex, punishable by three years in prison, and suggested deleting the crimes of “aiding and abetting homosexuality,” and "conspiracy to commit homosexuality", but included a penalty of seven years in prison for "procuring homosexuality by threats".

Bahati said he would not be pushing for the death penalty but the focus would now be primarily on targeting the “promotion” of homosexuality, which could extend to public health policies. The Most at Risk Populations’ Initiative, introduced in 2008 by the Ministry of Health to target HIV counselling and prevention toward specific populations, including MSM, could, for instance, see health practitioners and members of civil society imprisoned.

Bahati said the bill had the support of an overwhelming number of MPs and he expected it to be debated and passed by the end of the year. Stephen Tashobya, chairman of the Committee of Parliamentary and Legal Affairs, said the bill could, in theory, be tabled any time from next week, but that the government agenda would take precedence.

However, even if passed, the bill would require assent from President Yoweri Museveni, who holds strong views against homosexuality but amid international condemnation last year said he would not back a bill with either death penalty or “aggravated homosexuality” provisions.

Nevertheless, activists say a weaker version of the bill would retain the illegal nature of homosexuality and keep gays and lesbians in the closet while encouraging dangerous stigma against them in society. Homosexual Ugandans say they live in fear, especially following the murder of prominent gay activist David Kato in 2010 shortly after he was “outed” by a local tabloid.

HIV Prevention and Control Bill
Also left pending by the previous session of parliament and likely to be carried over into the next session is the HIV Prevention and Control Bill (2008), intended to provide a legal framework for the national response to HIV, as well as protect the rights of individuals affected by HIV. However, certain provisions—such as punishing the deliberate transmission of HIV with the death penalty—have been heavily criticized by human rights activists, who claim they would only serve to increase stigma and discrimination against people living with HIV.

Attacks on people living with HIV are also not uncommon, with several acts of aggression and murder reported in the press over the past few years.

Major Rubaramira Ruranga, executive director of the National Guidance and Empowerment Network of people living with HIV/AIDS in Uganda, says if passed, the bills would breed an environment of distrust and secrecy around an epidemic that benefits from open dialogue.

"People need to be counselled, people need to take informed decisions to disclose their HIV status," he said. "Above all, it creates a situation where people do not want to present themselves to health institutions, even for HIV testing."

The opposition politician and vocal HIV-positive activist said some of the two bills’ most harmful provisions were a blatant denial of human rights.

"They do not consider certain people to belong to society, they look at certain people as sinners, as criminals – and that kind of discrimination is anti-people," Ruranga said.
A Killer That’s Easy to Thwart
Washington Post, (05.03.2011) Laura Ungar
Before Pap screening began in the 1940s, about 26,000 US women died annually of cervical cancer. Incidence since has steadily dropped, from 14.2 cases per 100,000 population in 1973 to 8.1 per 100,000 in 2003-07. Today about 12,000 US women each year are diagnosed with cervical cancer, and 4,000 die of the disease.

Cervical cancer is highly correlated with poverty and inadequate or no health insurance, say experts including Robert Hilgers, a gynecologic oncologist in Kentucky. In the state’s Appalachia region, the 24.5 percent poverty rate is nearly double the national rate of 13.5 percent. Women there get cervical cancer at about one-third higher than the national rate and their death rate is about 37 percent higher, according to the Kentucky cancer registry and National Cancer Institute.

“In most cases, women who get cervical cancer in this country are those who did not get a Pap smear,” said Hilgers. “Socioeconomic factors that people live under affect their health.”

About half of newly diagnosed cervical cancers in the United States were among women who had not had a Pap test in five years, the Agency for Healthcare Research and Quality says. In 2008, about 83 percent of insured US women 18 or older had received a Pap smear within the previous three years, compared with 67 percent for the uninsured.

A program that can help screen low-income and under- and uninsured women is CDC’s National Breast and Cervical Cancer Early Detection Program. More efforts to bring testing directly to underserved populations would help, said New York gynecologist Shobha Krishnan, president of the Global Initiative Against HPV and Cervical Cancer.

So would access to the HPV vaccine, which protects against cervical cancer. “If everyone had the vaccine, that would stamp [cervical cancer] out,” said Dr. A. Bennett Jenson, who helped develop the vaccine.

Longitudinal Associations Among Relationship Factors, Partner Change and Sexually Transmitted Infection Acquisition in Adolescent Women
Sexually Transmitted Diseases Vol. 38; No. 3: P. 153-157, (03.11.2011) Mary A. Ott; Adrian Katschke; Wanzhu Tu; J. Dennis Fortenberry
Even when the partnerships do not overlap, new sex partners put adolescents at increased risk for sexually transmitted infections. In the current study, the authors prospectively examined associations between relationship characteristics, partner change, and subsequent STI during periods of “serial monogamy.”

In a longitudinal study, 332 adolescent females were interviewed and tested for gonorrhea, chlamydia, and trichomonas every three months for up to slightly more than six years. The interviews dealt with partner-specific relationship characteristics and sexual behaviors. The unit of analysis was the quarterly interval: a three-month period bracketed by interviews and STI testing. The researchers used a series of mixed regression models, controlling for age, STI at Time 1, and condom nonuse to examine the associations among relationship factors, partner change, and subsequent STI.

The factors that predicted partner change from Time 1 to Time 2 were age, lower relationship quality and lower levels of partner closeness to friends and family. Partner change was associated with acquisition of a new STI at Time 2.

“Although relationship factors did not exert a direct effect on STI at Time 2, they improved partner change-STI model fit. Similar patterns were seen with each organism,” the authors wrote. “Relationship factors drive partner change, which in turn contributes to STI acquisition. STI prevention research may need to focus on the relationship antecedents to partner change, in addition to the partner change itself.”

CMV Vaccine Clears SIV in Monkeys
SUMMARY
Macques given a CMV vector vaccine showed sustained CD8 T-cell activation, which was associated with control of a virus related to HIV.

As reported in the May 11, 2011, advance online edition of Nature, investigators tested a vaccine designed to protect against simian immunodeficiency virus (SIV), a relative of HIV that infects non-human primates.
The vaccine, consisting of SIV antigens combined with a cytomegalovirus (CMV) vector, stimulated an ongoing memory T-cell immune response, which appeared to inhibit mucosal SIV infection at the earliest stages. Nearly half of the macaques that received the CMV vaccine either alone or followed by an adenovirus vector vaccine demonstrated "early complete control" of SIV; 12 of these 13 monkeys showed protection lasting at least 1 year.

Below is an edited excerpt from a press release issued by Oregon Health and Science University explaining the research and its findings.

Non-Human Primate Studies Reveal Promising Vaccine Approach for HIV

Hillsboro, OR—May 11, 2011—Research conducted at Oregon Health and Science University’s Vaccine and Gene Therapy Institute (VGTI) has developed a vaccine candidate in non-human primates that may eventually lead to a vaccine against Human Immunodeficiency Virus (HIV). Details of this advance are published in the advance online edition of the journal Nature. The paper will also be published in an upcoming print addition of the journal.

The research team, led by Louis Picker, MD, associate director of the OHSU VGTI and director of the VGTI’s vaccine program, produced a vaccine candidate that programs the immune system of non-human primates to respond more swiftly to the presence of a primate version of HIV than it normally would. The team also included researchers from the National Cancer Institute-Frederick and the International AIDS Vaccine Initiative.

The VGTI researchers tested their vaccine candidate in rhesus macaque monkeys at the Oregon National Primate Research Center using a monkey form of HIV called Simian Immunodeficiency Virus (SIV). Of the monkeys that received the vaccine candidate, just more than half controlled replication of the virus to the extent that even the most sensitive tests could not detect signs of SIV. To date, the vast majority of these animals have maintained control over the virus for more than a year, gradually losing any signs that they had ever been infected. In contrast, the macaques in the unvaccinated control group developed the monkey form of AIDS.

The researchers say that their work suggests that the immune responses elicited by this new vaccine candidate might completely clear SIV from animals that were initially infected. In comparison, antiretroviral therapy is able to control the disease, but cannot clear the virus from its hiding place within the immune systems own cells.

The VGTI team has been working for over ten years on its vaccine candidate, which is unique in using cytomegalovirus (CMV) as the transport system used to introduce the vaccine into the body. CMV was chosen because it is believed that most people are already infected with CMV, but for the majority, the virus causes little or no symptoms. In addition, once a person is infected with CMV, this virus remains in the body for life. Picker and his team hypothesized that if such a persistent virus were used as a vector it could create and maintain resistance against HIV by programming a portion of the body’s immune system called effector memory T-cells to be constantly on the alert for the virus.

"The next step in vaccine development is to test the vaccine candidate in clinical trials in humans. For a human vaccine the CMV vector would be weakened sufficiently so that it does not cause illness, but will still protect against HIV," said Dr. Picker. 5/17/11

Reference

Vitamin D Linked to HIV Disease Progression

A growing body of evidence indicates that low vitamin D levels are common and can lead to detrimental health effects in people with HIV as well as the population at large.

Vitamin D may be obtained through food and is produced by the body when the skin is exposed to sunlight. Darker skinned individuals and people who live in colder climates where less skin is exposed are more prone to low levels.

As described in the April 25, 2011, advance online edition of AIDS, Jean-Paul Viard and fellow investigators with the EuroSIDA Study Group examined the association between vitamin D levels and disease progression in HIV positive people.
The study included 2000 participants in the large EuroSIDA study from Europe and Argentina who were randomly selected for vitamin D measurement using stored plasma samples. Participants were taking combination antiretroviral therapy (ART).

Levels of 25-hydroxyvitamin D, or 25(OH)D—the precursor to the physiologically active form—were stratified into tertiles, or thirds (,< 12, 12–20, and > 20 ng/mL). The researchers analyzed factors associated with low vitamin D levels, as well as associations between vitamin D and AIDS-related events, non-AIDS events, and all-cause mortality. Participants were followed for a median of 5 years.

**Results**

Among 1985 participants with vitamin D levels available:

- 23.7% had 25(OH)D < 10 ng/mL, or deficient;
- 65.3% had levels between 10 and 30 ng/mL, or low;
- 11.0% had > 30 ng/mL, or normal.

The following factors were significantly associated with greater likelihood of low vitamin D levels:

- Older age;
- Black race/ethnicity;
- Living outside southern Europe or Argentina;
- Blood samples obtained during winter;
- HIV transmission route other than male-male sex (i.e., injection drug use or heterosexual transmission).

Conversely, participants taking HIV protease inhibitors were less likely to have low vitamin D.

Compared to those in the lowest 25(OH)D tertile, those in the middle and highest tertiles had significantly lower risk of clinical disease progression during follow-up:

- AIDS-related events occurred in 10% of people in the lowest, 6% in the middle, and 5% in the highest tertile; adjusted incidence rate ratio 0.58 for middle tertile and 0.61 for highest tertile, or about 40% lower risk.
- All-cause mortality rates were 11% in the lowest, 7% in the middle, and 6% in the highest tertile; adjusted incidence rate ratios 0.68 and 0.56, respectively.
- Non-AIDS events occurred in 9%, 7%, and 7%, respectively, representing a slight but non-significant reduction in the middle and highest tertiles.

There were no significant differences between people in the middle vs highest tertiles for any of these outcomes.

Based on these findings, the study authors wrote, "25(OH)D deficiency was frequent in HIV-infected persons (83% on combination ART), and was independently associated with a higher risk of mortality and AIDS events."

Studies across Europe have found vitamin D levels below 10 ng/mL in 2% to 30% of adults in the general population, they noted in their discussion. The U.S. SUN study found that about 30% of HIV positive people had levels below 20 ng/mL, compared with about 40% of participants in the NHANES general population survey. Thus "vitamin D deficiency might not be more frequent in people living with HIV than in the general population."

The EuroSIDA investigators did not see a link between use of ART overall or efavirenz (Sustiva) and lower vitamin D levels as suggested in some prior studies. The observed link between protease inhibitor use and higher 25(OH)D levels "is of unclear biological relevance," they wrote.

Having the lowest vitamin D levels remained strongly associated with AIDS-related events and all-cause mortality even after adjusting for a large number of variables including season, race/ethnicity, geographic origin, CD4 cell count, HIV viral load, anemia, and kidney function (eGFR).
"Vitamin D deficiency therefore represents a new, independent, unfavorable prognostic marker in HIV infection, but without further research this cannot translate into clinical recommendations," the authors concluded.

"These results provide strong evidence that vitamin D deficiency is an important cofactor in HIV disease progression, even in the setting of widespread, efficient combination ART," they continued. "Whether the relationship between vitamin D deficiency and events is causal must now be addressed, because of potential public health consequences."

Reference

Haiti Presents Plan To Immunize 90 Percent Of Newborns
Haiti has a plan to vaccinate 90 percent of newborns by 2015, according to PAHO, but "[w]hether the plan works will depend on Haiti's ability to reverse decades of incompetent government and bad coordination among aid groups," as well as whether there will be funding, the New York Times reports.

The plan needs $100 million to be carried out, and even with approval from the GAVI Alliance, funding would still fall $21 million short, according to the newspaper. Under the plan, children would receive a pentavalent immunization that protects against Haemophilus influenzae type B, or Hib, hepatitis B, diphtheria, pertussis and tetanus, as well as vaccines against rotavirus and pneumococcal infections. If the plan is approved by GAVI, Haiti would be the last country in the Western hemisphere to adopt pentavalent vaccinations (McNeil, 5/16).

Deer tick bacteria DNA in joint fluid not reliable marker of active Lyme arthritis
Patients with persistent arthritis require more intensive antibiotic and DMARD therapy
New research shows that polymerase chain reaction (PCR) testing for Borrelia burgdorferi DNA—the spirochetal bacteria transmitted by deer ticks—in joint fluid may confirm the diagnosis of Lyme arthritis, but is not a reliable indicator for active joint infection in patients whose arthritis persists after antibiotic therapy. Findings of this study are published in Arthritis & Rheumatism, a journal of the American College of Rheumatology (ACR).

Lyme disease is caused by the B. burgdorferi bacteria, which is transmitted to humans by the bite of an infected blacklegged tick, commonly known as the deer tick. The characteristic erythema migrans skin rash—resembling a bull's-eye mark—is often the first sign of infection, along with symptoms such as headache, fever, and fatigue. Surveillance data from the Centers for Disease Control and Prevention (CDC) report more than 30,000 new cases of Lyme disease each summer in the U.S., with 93% of cases occurring in Connecticut, Delaware, Massachusetts, Maryland, Minnesota, New Jersey, New York, Pennsylvania, Rhode Island, and Wisconsin. If left untreated, roughly 60% of patients will develop Lyme arthritis, which commonly affects the knee.

"Currently, the primary use for PCR testing in Lyme disease is to establish if active infection remains in patients with persistent arthritis following antibiotic therapy," said Allen Steere, M.D., Director of Clinical Research, Rheumatology Unit, at Massachusetts General Hospital and Harvard Medical School in Boston. "Our study goal was to determine the B. burgdorferi burden and viability in skin and joints of patients with Lyme disease." Researchers used PCR techniques to detect the deer tick bacteria DNA in skin samples of 90 patients with confirmed Lyme disease and in joint fluid or synovial tissue samples from 63 patients with Lyme arthritis, 23 who were responsive to antibiotics and 40 with antibiotic-refractory arthritis. In addition, both bacterial DNA and RNA were searched for in a subgroup of these patients.

In most patients, erythema migrans skin lesions, an early disease manifestation, yielded positive culture and PCR results for the Lyme disease agent. Similarly, the majority of pre-treatment synovial fluid samples in patients with Lyme arthritis, a late disease manifestation, had positive PCR results for B. burgdorferi DNA. Patients with Lyme arthritis were treated with oral antibiotics for one or two months, and in those for whom the arthritis did not resolve, IV antibiotics were administered for an additional month. If they had persistent arthritis despite three months of antibiotics, patients were treated with non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs).

About 30% of patients with persistent arthritis, despite the three month antibiotic regimen, still had positive PCR results for 4-9 months after the start of antibiotics. However, positive PCR results in the post-antibiotic period did not correlate with relapse or duration of arthritis. Moreover, synovial tissue...
samples obtained in the patients who underwent synovectomies for persistent arthritis more than one year after they first received antibiotics, in all cases, had uniformly negative culture and PCR results.

Researchers also detected B. burgdorferi mRNA, a marker of the bacterium viability, in 8 of 10 erythema migrans skin samples, but in none of 11 synovial fluid samples, including those taken prior to antibiotic treatment. Thus, the authors showed that the bacteria in erythema migrans samples were active and viable, while those in synovial fluid were near-dead or dead at any time point during the testing. “Our results confirm that detection of the bacteria which causes Lyme disease in synovial fluid is not a reliable test of active joint infection,” Dr. Steere concluded. "We recommend treatment of patients with Lyme arthritis with appropriate oral and if necessary, IV antibiotics for two to three months. However, in those with persistent arthritis despite oral and IV antibiotics of this duration, we then give DMARD treatment."


Gut Bacteria Linked to Behavior: That Anxiety May Be in Your Gut, Not in Your Head
ScienceDaily (May 17, 2011) — For the first time, researchers at McMaster University have conclusive evidence that bacteria residing in the gut influence brain chemistry and behaviour.

The findings are important because several common types of gastrointestinal disease, including irritable bowel syndrome, are frequently associated with anxiety or depression. In addition there has been speculation that some psychiatric disorders, such as late onset autism, may be associated with an abnormal bacterial content in the gut.

"The exciting results provide stimulus for further investigating a microbial component to the causation of behavioural illnesses," said Stephen Collins, professor of medicine and associate dean research, Michael G. DeGroote School of Medicine. Collins and Premysl Bercik, assistant professor of medicine, undertook the research in the Farncombe Family Digestive Health Research Institute.

The research appears in the online edition of the journal Gastroenterology.

For each person, the gut is home to about 1,000 trillion bacteria with which we live in harmony. These bacteria perform a number of functions vital to health: They harvest energy from the diet, protect against infections and provide nutrition to cells in the gut. Any disruption can result in life-threatening conditions, such as antibiotic-induced colitis from infection with the "superbug" Clostridium difficile.

Working with healthy adult mice, the researchers showed that disrupting the normal bacterial content of the gut with antibiotics produced changes in behaviour; the mice became less cautious or anxious. This change was accompanied by an increase in brain derived neurotrophic factor (BDNF), which has been linked, to depression and anxiety.

When oral antibiotics were discontinued, bacteria in the gut returned to normal. "This was accompanied by restoration of normal behaviour and brain chemistry," Collins said.

To confirm that bacteria can influence behaviour, the researchers colonized germ-free mice with bacteria taken from mice with a different behavioural pattern. They found that when germ-free mice with a genetic background associated with passive behaviour were colonized with bacteria from mice with higher exploratory behaviour, they became more active and daring. Similarly, normally active mice became more passive after receiving bacteria from mice whose genetic background is associated with passive behaviour.

While previous research has focused on the role bacteria play in brain development early in life, Collins said this latest research indicates that while many factors determine behaviour, the nature and stability of bacteria in the gut appear to influence behaviour and any disruption, from antibiotics or infection, might produce changes in behaviour. Bercik said that these results lay the foundation for investigating the therapeutic potential of probiotic bacteria and their products in the treatment of behavioural disorders, particularly those associated with gastrointestinal conditions such as irritable bowel syndrome.


Foot and Mouth Disease May Spread Through Shedding Skin Cells
ScienceDaily (May 16, 2011) — Skin cells shed from livestock infected with foot and mouth disease could very well spread the disease.
In a new paper appearing in the *Proceedings of the Royal Society B*, Lawrence Livermore National Laboratory scientist Michael Dillon proposed that virus-infected skin cells could be a source of infectious foot and mouth disease virus aerosols. His proposal is based on the facts that foot and mouth disease virus is found in skin and that airborne skin cells are known to transmit other diseases.

The proposal could lead to new methods for surveillance for foot and mouth disease (as in settled dust), the development of more effective control measures, and improved studies of the persistence of the disease in the environment. The research also may be applicable to how other infectious diseases are spread.

Foot and mouth is a highly contagious viral disease capable of causing widespread epidemics in livestock. The foot and mouth disease virus (FMDV) has multiple known routes of transmission. These include direct contact (animal-to-animal contact at mucous membranes, cuts or abrasions), indirect contact (such as contaminated bedding), ingestion (contaminated feed) and the respiratory or airborne pathway (inhalation of infectious aerosols).

"The airborne pathway may play a role in some outbreaks by causing disease 'sparks' (disease spread to regions remote from a primary infection site)," Dillon said. "If the disease isn't detected quickly, these 'sparks' can lead to major outbreaks."

Dillon cited the widespread dissemination of FMDV during the catastrophic 2001 United Kingdom outbreak, which is thought to be caused by the inadvertent transport of animals with unrecognized FMDV infection from a Prestwick area farm to areas previously free of FMDV.

Mammals actively shed skin cells into the environment. Skin cells comprise a significant fraction (1 percent to 10 percent) of measured indoor and outdoor aerosols and indoor dust. These cells; and the bacteria, yeast, fungi and viruses known to be present on the surface of (or in some cases inside) skin cells; can become airborne by being shed directly into the air or when dust is disturbed.

"Infectious material can become airborne on skin cells and cause infection when inhaled or deposited directly onto the skin of the new host," Dillon said. "This is believed to be a significant source of bacterial infection for surgical procedures and other infections that are a result of treatment in a hospital."

"While not a typical site for the initial FMDV infection, the skin is a major viral replication site in most animals," Dillon said. "The outermost layer of FMDV-infected skin needs to be analyzed to find out how stable the virus is in these skin cells."

Dillon’s proposal suggests a number of practical possibilities for FMDV surveillance and control:

- The sampling and management of settled dust could prove to be a useful tool for disease surveillance and control.
- Slaughtered animals may emit airborne FMDV via infected skin cells simply by exposure to wind and/or mechanical abrasion (e.g. moving animal carcasses, spraying hides with water).
- Airborne emissions from cattle and sheep may need to be revisited as infected skin cells trapped in hair may later become airborne (currently these animals are believed to contribute little to aerosol emissions relative to swine).

"Given the potential for skin cells to protect infectious virus from the environment, the management of other viral diseases may also benefit from enhanced dust surveillance and management, and skin decontamination," Dillon said.

**Journal Reference:**


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South African women with AIDS conspiracy beliefs half as likely to use condoms

Roger Pebody

Published: 18 May 2011

In Cape Town, African women who think that AIDS is man-made are half as likely as other African women to have used a condom during their most recent sexual encounter, researchers report in the journal *AIDS and Behavior*. In addition, African men who believe that HIV is harmless while antiretroviral drugs are harmful are half as likely to use condoms as other men.

There are important differences in the findings for men and women, which suggests that gender is crucial to understanding AIDS conspiracy and denialism in South Africa.

A previous ethnographic study has also found that the attribution of blame for HIV and AIDS expressed the different concerns of men and women. Women’s accounts centred on the domestic context,
whereas men—who had had greater exposure to international economic and political forces beyond their control—tended to blame more distant agents such as scientists, governments, soldiers and Americans.

For the current study, Eduard Grebe and Nicoli Nattrass analysed responses to the 2009 Cape Area Panel Study, a cross-sectional survey of young adults aged 19 to 29 in metropolitan Cape Town. They believe their sample is broadly representative of urban Africans and coloureds of the age group in this area.

A total of 2,901 individuals took part, 45% of whom were described as African, 49% as coloured and 5% as white.

Respondents were asked if they agreed or disagreed with three statements associated with AIDS conspiracy beliefs—that AIDS was invented to kill black people, that AIDS was created by scientists in America and that AIDS was deliberately created by humans. Individuals who agreed with more than one statement were considered to have AIDS conspiracy beliefs.

Whereas only 2.6% of non-Africans held conspiracy beliefs, one in five (19.7%) of young adult Africans did so.

The rest of the results we report only concern the 735 African women and 578 African men in the sample. Moreover, they are statistically significant results from multivariate analysis, which is adjusted for confounding factors.

Among African women, holding conspiracy beliefs was associated with lower levels of education and lower household income, but there was no clear association with employment or age. Members of religious organisations were half as likely to have conspiracy beliefs as other women.

However women who had scored highly for psychological distress (frequent experience of nervousness, hopelessness, worthlessness, depression etc) were twice as likely to hold conspiracy beliefs as other women (odds ratio 2.52, 95% confidence interval 1.33—4.76).

There were very strong correlations between beliefs in witchcraft, beliefs in the importance of initiation rituals for men and AIDS conspiracy beliefs.

Women who had never heard of the Treatment Action Campaign (a group which has campaigned vigorously against conspiracy theories) were three times as likely as others to hold conspiracy beliefs. On the other hand, women who often got news from TV, radio or newspapers were actually more likely to hold conspiracy beliefs than others.

Whereas the researchers identified a number of factors that are associated with women holding conspiracy beliefs, the picture is less clear-cut for African men. For the majority of the factors previously cited, there were no statistically significant associations between the factors and having conspiracy beliefs.

However the association with psychological distress was equally important (odds ratio 3.01, 95% confidence interval 1.41—6.41).

And whereas women who got news from the TV, radio or newspapers tended to hold conspiracy beliefs, men using the media are less likely to hold these beliefs.

AIDS beliefs and condom use
Respondents were asked whether a condom had been used during their last sexual encounter. In terms of conspiracy beliefs, the picture is once again different for African women and men.

Women holding conspiracy beliefs were half as likely as other women to have used a condom (odds ratio 0.55, 95% confidence interval 0.32—0.94).

For African men, the results were not statistically significant (odds ratio 0.84, 95% confidence interval 0.47—1.51).

about AIDS denialism were also assessed during the survey. Respondents who believed both that HIV is harmless and that antiretroviral drugs do more harm than good were classed as having AIDS denialist beliefs, and this was the case for 18.4% of African respondents.

Whereas there were no associations between AIDS denialism and condom use for women, men with denialist beliefs were half as likely to have used a condom the last time they had sex (odds ratio 0.45, 95% confidence interval 0.26—0.77).

This study builds on previous South African research which demonstrated that AIDS conspiracy beliefs were associated with lower rates of HIV testing. The current authors note that “political divisions over AIDS continue to matter via their negative impact on safe sex”.

Reference
China hospitals deny help to HIV/AIDS patients: UN
(AFP) – 15 hours ago
BEIJING — People living with HIV/AIDS in China are routinely denied medical treatment in hospitals, a UN agency said Wednesday, in a sign of ongoing discrimination despite recent progress.

The International Labour Organization (ILO) uncovered HIV-related discrimination in China's hospitals and clinics via interviews with more than 100 people living with HIV, and 23 hospital managers and healthcare workers.

One 37-year-old man living with HIV—the virus that causes AIDS—from the northern province of Shaanxi said he had huge difficulties getting treatment when he found a lump in his stomach.

"Each hospital advised that I should be hospitalised immediately for surgery, but when they heard that I was HIV-positive, none were willing to accept me. They asked me to go to the infectious diseases hospital," he was quoted as saying.

"That hospital did not agree to let me use the operating theatre. They said if other patients knew that an HIV person had used the operating theatre, it would badly influence the hospital's reputation."

According to Chinese authorities, at least 740,000 people have HIV/AIDS in the country, out of a total population of 1.3 billion, although advocates for patients believe the real figure could be much higher.

Those living with HIV/AIDS have long faced discrimination, but there has been progress as the government has started talking more openly about HIV prevention and control.

According to the ILO report, HIV-related discrimination in Chinese hospitals is triggered by two major factors.

Many general clinics systematically refer HIV patients to specially designated hospitals for infectious diseases. But they must only be sent there if they require treatment linked to HIV/AIDS, not for an unrelated condition.

Hospitals in China are also primarily driven by profit, and the report said hospital management was sometimes worried that prospective patients would go elsewhere if they knew the hospital provided services for people with HIV.

The Chinese government has already identified this issue as an area requiring stronger policy implementation, the report added.

But the ILO called for better regulations and better awareness among hospital management about the rights of people living with HIV/AIDS to access medical services.

Clinics Discourage Zambian Youth From Sexual and Reproductive Health Services
In Zambia, young people say that unfriendly health workers at local clinics discourage them from seeking the information and services they need when it comes to sex. The results are high teenage pregnancy and fertility rates and low knowledge of HIV/AIDS. The government and nongovernmental organizations have recognized this gap and aim to close it.

by Chanda Katongo Reporter, Tuesday—May 17, 2011
LUSAKA, ZAMBIA — Natasha, a student in her third year at the University of Zambia in Lusaka, the capital, says she will never forget the way a health worker at a local clinic scolded her when she went there seeking sexual and reproductive health information and services.

Natasha, who declined to use her full name for privacy reasons, says she went to the clinic for information on contraception. But she says the nurses there said that they were reluctant to help her because she was not married and too young to be seeking family planning information and services.

“I had been reacting to the contraceptives that I had been taking, and when I went to the clinic and explained to the health worker what my problem was, she told me I was too young to be using contraception and that I should be abstaining because I am not married,” Natasha says.

Natasha says the health worker began to question her.

“She asked me why I was not abstaining [from sex] and I said that if she knew my parents she would have told them that I am a naughty and stupid girl,” she says.

Natasha says her experience with health worker was hurtful and will discourage her from going back.

“I felt so bad and so out of place that day,” Natasha says. “The nurse made me feel so guilty.”

She says her friends have had similar experiences when trying to obtain sexual and reproductive health care and information.

“When I told my friends about it, they asked me why I had even bothered to go the clinic because some of them had also experienced unfriendly treatment at different clinics as well,” she says.
In Zambia, young people say that health workers at clinics discourage them from obtaining sexual and reproductive health services because they aren’t married. Doctors and activists say more training is needed to make health workers more receptive to the younger generation. The government has acknowledged the gap in services for the young and has begun to develop a strategy to address it, as have multiple nongovernmental organizations, NGOs, and global campaigns.

Like in other countries around the world, the provision of sexual and reproductive health services to young people in Zambia – although legal – is still a sensitive issue. Yet it’s become an important topic as the country has been undergoing rapid population growth, which has put pressure on already overburdened socio-economic resources, especially in regards to education, health and food security, according to Muyambo Sipangule, Zambia’s deputy permanent representative to the United Nations.

High fertility levels have led to rapid population growth here, Sipangule said last month at the 44th Session of the U.N. Commission on Population and Development. Zambia’s population has grown from 5.6 million in 1980 to 13 million in October 2010, thanks to a high total fertility rate, or average number of births per woman, of 6.2 as of 2007.

Teenage pregnancy is also high in Zambia, with about three in 10 women beginning childbearing between ages 15 to 19, according to the most recent Zambia Demographic and Health Survey, ZDHS, from 2007. Overall, less than 35 percent of Zambians ages 15 to 19 had comprehensive knowledge of HIV/AIDS, according to the ZDHS, while more than 15 percent of the population here is HIV-positive.

The majority of young people surveyed said they knew of a condom source, but many say it is difficult to obtain sexual and reproductive health services. They say that health workers at clinics, hospitals and other health centers tend to be unfriendly toward them, making them less likely to return in the future for the information and services they need.

A nurse at the University Teaching Hospital, UTH, Zambia’s largest hospital, who requested anonymity to protect her job, says she doesn’t understand why a young person would seek family planning information. She says that young people who are unmarried should abstain from sexual activity.

―If these so-called young people were abstaining as they should, they would not have to go looking for health services that are meant for adults and married couples,‖ she says.

The nurse says that the media is to blame.

―The problem with young people is that they like to try what they watch on television,‖ she says.

Remmy Shawa, global youth coordinator for the World AIDS Campaign, which aims for universal, nondiscriminatory and nonjudgmental access to HIV prevention, treatment, care and support, says that non-youth-friendly health services are an obstacle to them attaining the care they need.

―Usually there is what is called age discrimination, where the health service provider – mostly an adult – believes that young people should not suffer from certain illnesses,‖ Shawa says. ―So when a young person presents with such an illness, the provider becomes judgmental and sometimes tries to admonish that young person.‖

He says this discourages them from seeking the care they need in the future when it comes to pregnancy, sexually transmitted infections, STIs, HIV/AIDS and more.

―Such interactions make it hard for that young person and many others to go back for those services,‖ he says.

Shawa attributed the non-youth-friendly health services to the linking of public health and morality by many service providers.

―In a country like Zambia, which is a Christian nation, a young person is supposed to stay away from sex [un]til marriage,‖ Shawa says. ―Thus, if a young person goes to the clinic or any health center with an STI, then he/she is immoral in the eyes of most service providers.‖

Shawa says that another problem is ignorance.

―Health service providers are simply ignorant about new developments and challenges that young people face,‖ Shawa says. ―Hence, they find it hard to understand and relate with young people.‖

A UTH doctor, who asked to remain anonymous to protect his job, says that the country lacks frequent and regular trainings and retrainings of health workers across the country on the importance of providing youth-friendly health services.

He says that improving their salaries and general working conditions could also help change the unfriendly attitudes displayed by some health workers.

Shawa says that more advocacy and awareness campaigns with service providers are needed to make health service providers more accommodating to young people.
“I believe that a youth-friendly service provider does not necessarily need to be a young person,” Shawa says. “Even an adult can be youth-friendly as long as they are trained on how to reach out to the young generation.”

Sipangule says the government has set up the Reproductive Health Commodity Security Committee and has begun to use community-based agents to increase the flow of reproductive health commodities, services and information around the country. He said modern family planning has gradually increased among married women, but that further effort and support were required to continue to increase access to and use of family planning services for women in rural areas and young people.

“Zambia recently carried out a situation analysis on reproductive health services for the adolescents and young people in the country, which identified the gaps, such as high teenage pregnancies, inadequate access to reproductive health services and information,” he said. “A strategy to address the gaps identified is being developed.”

Sipangule said the government had also recently revised its National Population Policy and was developing implementation framework, but asked for the United Nations’ continued support in its goal to lower the fertility rate.

In addition to global efforts, such as the World AIDS Campaign, Zambian NGOs, such as Youth Vision Zambia, a youth-led NGO in Lusaka dedicated to providing sexual and reproductive health information services to youth, are also working to educate and equip youth to protect themselves.

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UN: Homophobic-Based Hate Crimes on Rise

United Press International, (05.17.2011)

In a statement marking Tuesday’s designation as International Day Against Homophobia and Transphobia, the UN High Commissioner for Human Rights called on governments to do more to end
discrimination based on sexual orientation and gender identity. Navi Pillay said that while most other forms of prejudice “are universally condemned by governments, homophobia and transphobia are too often overlooked.” Statistics show that homophobic crimes are on the rise in many parts of the world, Pillay said, and more than 70 countries continue to criminalize homosexuality. UNAIDS Executive Director Michel Sidibe also issued a statement, noting that discrimination against sexual minorities hinders effective responses to the HIV/AIDS epidemic.

**CSI for Infection: Geographic Profiling, Used in Hunt for Serial Killers, Can Help Combat Infectious Diseases**  
ScienceDaily (May 17, 2011) — Every 30 seconds, infectious diseases such as malaria, HIV/AIDS and tuberculosis kill as many people as Jack the Ripper did in his entire career. New research published in BioMed Central’s open access journal *International Journal of Health Geographics* demonstrates how the mathematical model of geographic profiling, used in the hunt for serial killers, can help combat infectious diseases.

Geographic profiling is a statistical technique which uses the locations of crimes to identify areas in which the serial criminal is most likely to live and work, and was originally developed to help police prioritize suspects. Typically, such cases involve too many, rather than too few, suspects. For example, in the late 1970s police had to sort through over a quarter of a million names in the Yorkshire Ripper enquiry. Geographic profiling has been successfully used by law enforcement agencies around the world, including the Royal Canadian Mounted Police, Scotland Yard and the Bureau of Alcohol, Tobacco, Firearms and Explosives.

Now, research led by Dr Steven Le Comber in the School of Biological and Chemical Sciences at Queen Mary, University of London, has shown that this method can use the locations of disease cases to identify the source of the disease.

Dr Le Comber, in collaboration with scientists at the University of Miami and Ain Shams University in Cairo, as well as with the inventor of geographic profiling (former detective turned Professor of Criminal Justice Kim Rossmo from Texas State University), examined a classic study, the 1854 cholera outbreak in London, and more recent cases of malaria in Cairo. In both cases geographic profiling successfully located the sources of the disease—the Broad Street pump in London, and the breeding habitats of the mosquito Anopheles sergentii in Cairo.

"This is a very exciting development," said Dr Le Comber. "Correctly applied, geographic profiling shows great promise as a useful component of policy relating to the control of a wide variety of infectious diseases. Evidence-based targeting of interventions like this is more efficient, environmentally friendly and cost effective than untargeted intervention."

**Journal Reference:**  

**Vaccine Protects from Deadly Hendra Virus**  
ScienceDaily (May 17, 2011) — CSIRO scientists have shown that a new experimental vaccine helps to protect horses against the deadly Hendra virus.

Dr Deborah Middleton from CSIRO’s Australian Animal Health Laboratory (AAHL) announced the successful progress to develop the vaccine at the Australian Veterinary Association conference in Adelaide on May 17, 2011.

"Our trials so far have shown that the vaccine prevents the infection of horses with Hendra virus," Dr Middleton said.

Stopping the disease in horses could also help protect people from the disease.  
"A horse vaccine is crucial to breaking the cycle of Hendra virus transmission from flying foxes to horses and then to people, as it prevents both the horse developing the disease and passing it on," Dr Middleton said.

Hendra virus first appeared in 1994 and five of the 14 known outbreaks have spread to people. The virus has killed four of the seven people infected.

Depending on further development, field trials and registration the vaccine may be available as early as 2012.

Dr Barry Smyth, President of the Australian Veterinary Association, said that the news on the vaccine will be welcomed by both vets and horse owners.
"It's important that veterinarians and horse owners continue with precautions that reduce the risk of spreading the virus and that they report suspected cases immediately," Dr Smyth said.

Recent work on evaluating the vaccine was jointly funded by the CSIRO, the Australian Government Department of Agriculture, Fisheries and Forestry and the Queensland Government Department of Employment, Economic Development and Innovation.

The development of the vaccine goes back more than ten years to shortly after CSIRO scientists first isolated the virus following the first outbreak of the disease in Hendra, Queensland.

Development and source of the vaccine is the result of a close collaboration with Dr Christopher Broder of the Uniformed Services University of the Health Sciences (the US federal health sciences university) supported by the US National Institutes of Health, but the high bio-containment facility at AAHL was essential for evaluating its beneficial effects.

"Our bio-security facility at AAHL is the only laboratory in the world where this work could have been done. It has been slow, painstaking and high-risk work and the credit is due to many people who've worked on this since 1994," Dr Middleton said.

**Novel vaccine did not protect monkeys against infection – but may have cured them**

Gus Cairns

Published: 19 May 2011

A novel vaccine using the common virus cytomegalovirus (CMV) as the vector or container of proteins from the simian immunodeficiency virus (SIV) protected none of a group of 24 rhesus macaques from infection. But in 13 of the monkeys vaccinated, it did produce infections characterised by an undetectable viral load.

This profound viral suppression led to an apparent decline in the number of SIV-infected cells over a period of two years after infection to the point that SIV-infected cells were undetectable in 72% of monkeys with controlled viremia. Despite this, there was no apparent waning of immune responses to SIV in the all-important effector-memory CD8 and CD4 lymphocytes over this time in twelve of the 13 monkeys.

The researchers comment that their vaccine seems to have produced "an unprecedented level of SIV control and even the possibility of progressive clearance of SIV infection over time."

The question now is how to make a safe analogue of this vaccine for use in humans.

**The vaccine**

The vaccine tested enclosed SIV components within the shell of another virus which establishes an ongoing but non-pathogenic infection. In this case they used CMV, which is a ubiquitous infection in rhesus monkeys and is present in about 50% of humans. The vaccine, therefore, acted not as a new viral infection but as a 'superinfection' of a new variety of CMV.

In this experiment, 24 rhesus macaques were given the novel CMV-vector vaccine, which contained the viral proteins gag, nef, rev, tat, env and parts of the polymerase (pol) protein. Twelve of these animals were given two doses of the CMV vaccine. The other twelve were given one dose of the CMV vaccine and then one dose of a more conventional adenovirus-vector vaccine containing the gag, pol, env and nef SIV proteins.

The 24 CMV-vaccinated animals were compared with nine animals given the adenovirus-vector vaccine alone. All vaccinated animals were then challenged, 13.5 months after the first vaccination shot, by rectal introduction of a highly-pathogenic SIV variant.

The course of infection was compared with 28 controls that were all unvaccinated but were challenged with SIV, eleven of whom were challenged with SIV at the same time as the vaccinated animals, while the other 16 had been challenged previously.

**The results**

The CMV vaccine did not work by protecting the animals against infection and indeed every single one of the challenged animals was infected, with no statistical difference in the number of challenges need to establish infection.

Interestingly, one of the control animals displayed a delayed infection, maintaining an undetectable viral load despite testing antibody-positive for SIV for the first 105 days. After this, however, SIV virus suddenly appeared in the blood and soon established itself at normal levels, and the subsequent course of infection was similar to that in the other controls.

However in just over half (13) of the CMV-vaccinated animals, the subsequent infection resembled those seen in 'elite controllers': after an initial spike of virus in the blood, they quickly achieved an almost-
complete control over their virus, maintaining viral loads under 30 copies/ml with occasional ‘blips’, usually to no more than 1000 copies/ml. The frequency of blips declined after week 30 post-infection from 1.5 blips per ten-week period to 0.1 per ten weeks, and then stayed at that frequency for the remainder of the 700-day follow-up period.

Immune responses in CD8 T-cells to the SIV gag and pol viruses remained strong throughout the follow-up period on CMV-vaccinated animals. In contrast responses to an SIV protein that was not contained in the vaccine, the vif protein, while starting out at the same levels, declined to 10% of its initial level over the 700 days.

The researchers hypothesised that this response to vif – which must be caused by the monkeys’ natural response to SIV – might be declining over time because the number of cells infected with SIV was declining.

This proved to be the case: after sacrificing four vaccinated animals, they tried to find cell-associated viral DNA in cells taken from the gut, lymph nodes and other tissues and found none in 72% of the animals. Excitingly, the levels of cell-associated DNA seen were almost indistinguishable from the proportion of ‘false positive’ DNA results seen in an uninfected animal and far lower – in the order of one DNA copy per 100 million cells – than the levels seen in two animals that had achieved long-term viral control in two previous vaccination experiments (about one DNA copy per half a million cells).

In the nine animals given the more conventional adenovirus vaccine, none achieved an undetectable viral load, but they did initially display a lower viral load that the control animals. However their viral load eventually returned to normal levels.

**Possible significance**

What is different about the CMV-based vaccine? Vaccines using viral vectors and ‘fake viruses’ are now almost commonplace. However previous vaccines using viruses such as adenovirus have produced inconsistent results in animals and in humans, the only large efficacy trial using a viral vector alone, the STEP trial, may actually have increased some people’s vulnerability to HIV. The more successful RV144 trial used another viral vector but the vaccine’s (rather weak) efficacy appeared to be generated by an antibody response to the other vaccine component, not to the viral vector.

The CMV vaccine stimulated immunity in a different group of T-cells. Previous viral vectors have stimulated immunity in the central memory T-cells that mainly dwell in sites like the lymph nodes. This vaccine however mainly stimulated immunity amongst the effector-memory T-cells that patrol the mucous membranes. The researchers hypothesise that the vaccine is able to interrupt the process of infection at an earlier stage, before the SIV has travelled to the lymph nodes and established a fully-productive infection.

However the researchers emphasised that there is a lot they still do not understand about the immune response seen to the CMV vaccine, exactly why it produced such a powerful response and, crucially, what distinguished the 13 monkeys who responded from the eleven who did not.

Vaccine researchers welcomed the study, but said that it might be difficult to manufacture a version of the vaccine that was safe to use in human studies, given that CMV can cause a number if significant illnesses, especially in people with AIDS and compromised immunity.

Professor Sir Andrew MacMichael of Oxford University told the BBC: "CMV is not totally benign, it does cause a number of diseases. If you’re giving people something you’re not going to be able to get rid of should it cause problems, then that’s quite a difficult risk to manage."

Lead Investigator Louis Picker of the Vaccine and Gene Therapy Institute in Oregon said in reply that 99% of people in sub-Saharan Africa are already infected with CMV. He said: "We know at lot about it and it’s mostly non-pathogenic, except in vulnerable populations like pregnant women." He added that his team were now looking to create a vaccine that had the same immune activity with a weakened version of CMV that could not cause harmful infection.

**Reference**


**What's HIV Got to Do With It? New York Post Violates Alleged Victim's Rights in Strauss-Kahn Case**

A brutal rape and sexual assault was not enough. Now the NY Post has turned its vicious sights on the woman who brought assault charges against IMF leader Dominique Strauss.

Rather than focus on the issue of this young woman’s assault charges against a high-powered diplomat, the NY Post chose to break a sensationalist, unfounded story speculating about the young
woman’s HIV status. A young, West African working-class immigrant and single mother, she surely experiences multiple forms of marginalization in our society and has shown commendable courage in coming forth with her story. Like anyone, she is entitled to justice, and physical and psychological safety for herself and her family during and after the process of justice.

The NY Post’s irresponsible coverage exacerbates the power dynamics of racism, sexism, and classism inherent between the woman who has brought charges of assault and Strauss-Kahn, a man in a position of great power. The coverage creates a chilling effect for women who may need to bring assault charges in the future against powerful people, especially for women of color, low-income women, and immigrant women.

These irrelevant and potentially false statements serve to intensify existing struggles that young women face daily and could result in violence or discriminatory treatment towards both the young woman in this case and her child. This type of reporting is irresponsible and downright dangerous. It perpetuates an environment in which people cannot feel safe coming forward as survivors of violence without having their sexual history, health status, and ultimately their credibility, questioned. What was the Post’s real motivation in breaking this story? Would the story have been the same if she were not a young, working-class West African immigrant?

The U.S. Positive Women’s Network (PWN), a national membership body of HIV-positive women and a project of Oakland-based women’s HIV organization WORLD, is outraged by the NY Post’s vicious attack on the woman who brought assault charges against IMF leader Dominique Strauss-Kahn “She is a woman of color who may have been raped physically and is now being raped again,” says Minister Antoinette Etienne, an HIV-positive woman, and member of the NYC HIV Planning Council.

“The young woman who came forward with rape and assault charges deserves safety and respect from the law enforcement community, media and advocates for her courage in speaking up for her rights.” PWN demands the NY Post publicly apologize for this story, not engage in this type of sensationalist journalism, and engage only in coverage that is relevant to the case.

STD Rates Soar Among Older Adults
Orlando Sentinel , (04.17.2011) Marni Jameson
Reported cases of syphilis and chlamydia among people ages 55 and older increased 43 percent from 2005 to 2009, CDC data show. Factors that may be driving the STD increase among older Americans include people living longer, healthier lives, and the introduction of sex-enhancing medicines such as Viagra. In addition, many seniors were never the target of safe-sex campaigns in the past, so their condom use is lower, say experts.

Though older Americans represent a small proportion of new STD diagnoses overall, they “face unique prevention challenges, including discomfort in discussing sexual behaviors with physicians and partners, and discomfort discussing condom use,” said Rachel Powell, a CDC spokesperson.

Dr. Connie Micklavzina, a gynecologist at Orlando’s Winnie Palmer Hospital for Women & Babies, said she has begun asking her older patients if they would like to be screened for STDs. “Often I see a huge look of relief on their faces, because they are too embarrassed to ask. The responsibility of bringing this up should be on the practitioner, not the patient, to make the conversation easier,” she said.

In February, the Centers for Medicare and Medicaid Services announced it is considering providing coverage for STD screenings as well as related behavioral counseling for seniors. Medicare already pays for HIV tests.

African Gays Under Attack as HIV/AIDS Epidemic Turns 30
Voice of America , (05.13.2011) Joe DeCapua
Though Uganda’s Parliament on Friday shelved a bill calling for the death penalty for homosexuals in certain cases, the situation for gays and lesbians there and in other areas of Africa remains precarious.

In January, well-known Ugandan gay activist and school teacher in Uganda David Kato was brutally murdered. Last year in Malawi, a gay couple was sentenced to 14 years hard labor after announcing their intention to marry. They were later released but ordered to have no further contact. Such incidents only help to prolong the continent’s HIV/AIDS epidemic, say experts.

“Whether you’re gay or straight, the odds of you going to get testing for HIV or seek care for HIV are very low because to do so might imply that you are a gay person,” noted Regan Hoffman, editor in chief of POZ magazine. “And if that can land you in jail for life, or you could be beaten and killed, why in God’s name would you go and seek your HIV status or seek care?”
David Kuria of the Gay and Lesbian Coalition of Kenya, who is featured in POZ, said gay men often must "either marry a woman or risk being killed." "In Kenya, it seems that men who lead double lives do so because they do not have a choice," he said.

According to Hoffman, Uganda’s HIV/AIDS efforts have suffered due in part to public officials’ homophobia. “Uganda was a role model for HIV prevention and care because they were aggressively treating it and treating people benevolently who had the disease,” she said. “I’m not sure exactly what happened in terms of Uganda’s reversal of rates. I know it had to do in some part with a change in public attitude and also governmental attitude about being open about sexuality and therefore sexually treated diseases.”

**Study Urges Three-Year Gap in Cervical Cancer Test**

*Agence France Presse*, (05.18.2011)

Women age 30 or older who have a negative human papillomavirus (HPV) test and a normal Pap smear could safely extend cervical cancer screening intervals to every three years, a new study suggests.

Researchers evaluated data involving 331,818 women who undertook co-testing at Kaiser Permanente Northern California. The women were followed for five years, and investigators charted the five-year cumulative incidence of cervical cancer and cervical intraepithelial neoplasia grade 3 (CIN3+).

Among women with both a normal Pap smear and a negative HPV test, the five-year cancer risk was "very low: 2.3 per 100,000 women per year,” the study said. In comparing the HPV test and Pap smear, the HPV test "identified more women at high risk for cervical cancer than Pap tests," researchers announced Wednesday ahead of the study’s presentation at the American Society of Clinical Oncology’s annual meeting in Chicago, June 3-7.

Women over 30 who test HPV-positive are usually retested in six months to see if they clear the virus.

“Our results are a formal confirmation that the three-year follow-up is appropriate and safe for women who have a negative HPV and normal [Pap] test result,” said lead author Hormuzd Katki.

“These results also suggest that an HPV-negative test result alone could be enough to give a high level of security for extending the testing interval to every three years,” Katki said. “But we’ll need additional evidence from routine clinical practice, and formal recommendations from guideline panels before that can be routinely recommended” for the general population, the researchers said.

The study, “Cervical Cancer Risk for 330,000 Women Undergoing Concurrent HPV Testing and Cervical Cytology in Routine Clinical Practice,” will be presented at the conference; the abstract is available at: http://abstract.asco.org/AbstView_102_83726.html.

**40 Percent of Pregnancies Across USA Unplanned, Study Finds**

*USA Today*, (05.19.2011) Sharon Jayson

According to the first analysis of its kind, about 40 percent of pregnancies in the United States are unwanted or mistimed. Mississippi led the nation with 69 unplanned pregnancies per 1,000 females ages 15-44, while the figure in New Hampshire, 36 per 1,000, was the lowest. The study was based on 2006 data from 86,000 women who gave birth and 9,000 who underwent abortion; it was published in the journal Perspectives on Sexual and Reproductive Health. More than half of all pregnancies in 29 states and the District of Columbia were unintended. In almost every state, 65 percent to 75 percent of unintended pregnancies were considered mistimed, while 25 percent to 35 percent were unwanted. “We do a better job of planning to buy tickets to see Lady Gaga than we do about being careful in planning for when we’re going to have children, how many children and when in our lives we’re going to have them,” said Claire Brindis, director of the Bixby Center for Global Reproductive Health at the University of California-San Francisco; she was not involved in the study.

**Wolbachia bacteria reduce parasite levels and kill the mosquito that spreads malaria**

*Wolbachia* are bacteria that infect many insects, including mosquitoes. However, *Wolbachia* do not naturally infect Anopheles mosquitoes, which are the type that spreads malaria to humans. Researchers at the Johns Hopkins Bloomberg School of Public Health found that artificial infection with different *Wolbachia* strains can significantly reduce levels of the human malaria parasite, *Plasmodium falciparum*, in the mosquito, *Anopheles gambiae*. The investigators also determined that one of the *Wolbachia* strains rapidly killed the mosquito after it fed on blood. According to the researchers, *Wolbachia* could potentially be used as part of a strategy to control malaria if stable infections can be established in Anopheles. Their study is published in the May 19 edition *PLoS Pathogens*.

"This is the first time anyone has shown that *Wolbachia* infections can reduce levels of the human malaria parasite (*Plasmodium falciparum*) in *Anopheles* mosquitoes," said Jason Rasgon, PhD, senior
author of the study and associate professor with the Johns Hopkins Malaria Research Institute and the Bloomberg School’s W. Harry Feinstone Department of Molecular Microbiology and Immunology.

For the study, Rasgon and his colleagues infected Anopheles gambiae mosquitoes with two different Wolbachia strains (wMelPop and wAlbB). After infection, Wolbachia disseminated widely in the mosquitoes and infected diverse tissues and organs. Wolbachia also seemed to actively manipulate the mosquito’s immune system to facilitate its own replication. Both Wolbachia strains were able to significantly inhibit malaria parasite levels in the mosquito gut. Although not virulent in sugar-fed mosquitoes, the wMelPop strain killed most mosquitoes within a day after the mosquito was blood-fed.

"These experiments show that Wolbachia could be used in multiple ways to control malaria, perhaps by blocking transmission or by killing infected mosquitoes," said Rasgon.

Worldwide, malaria afflicts more than 225 million people. Each year, the disease kills nearly 800,000, many of whom are children living in Africa.

**Packaging Process for Genes Discovered**

ScienceDaily (May 19, 2011) — Scientists at Penn State University have achieved a major milestone in the attempt to assemble, in a test tube, entire chromosomes from their component parts. The achievement reveals the process a cell uses to package the basic building blocks of an organism’s entire genetic code—its genome. The evidence provided by early research with the new procedure overturns three previous theories of the genome-packaging process and opens the door to a new era of genome-wide biochemistry research.

A paper describing the team’s achievement will be published in the journal Science on 20 May 2011.

The research was accomplished with the help of a new laboratory procedure developed by the team of scientists led by B. Franklin Pugh, the Willaman Chair in Molecular Biology at Penn State. The procedure allows scientists, for the first time, to do highly controlled biochemical experiments with all the components of an organism’s genome.

The team’s research is designed to reveal the construction process for the chromosome—the super-compressed marvel of molecular packaging that contains all an organism’s DNA and associated proteins. "Our procedure starts with an entire genome of DNA from yeast cells that we propagate through bacteria, then purify," Pugh said. "Next, we add equal parts of pure histones, the protein building blocks of chromosomes. Then we allow the assembly process to begin."

The result was that short sections of the lanky string of gene-containing DNA became wound around a series of histone proteins, forming a line of knots called nucleosomes separated by unknotted sections of DNA. Although earlier studies in other labs had shown that histones and DNA alone could construct a series of nucleosome knots along the DNA string, the overall structure of this construction was not nearly as organized as it needed to be in order to look like chromatin inside of a cell—the material that the cell remodels to form chromosomes. Pugh’s team sought out the recipe that would produce the actual, highly organized structure of chromatin.

"Just like baking a mixture of flour and water produces unleavened bread that lacks the texture of leavened bread, so too did the mixture of histones and DNA lack the texture of chromatin," explains Pugh.
New Way to Duplicate Immunity Boosting Cells to Unprecedented Levels

ScienceDaily (May 19, 2011) — University of Minnesota Medical School researchers have discovered a method to quickly and exponentially grow regulatory T-cells—also known as "suppressor cells." The new process enables replication of the cells by tens of millions in several weeks, a dramatic increase over previous duplication methods. Historically, regulatory T-cells have been difficult to replicate.

The new technique will give patients a better chance of having a successful bone marrow or organ transplant, and will have profound implications for patients with autoimmune diseases such as lupus, type 1 diabetes, Crohn's disease and multiple sclerosis.

The use of the new replication technique has already shown promising effects in the treatment of acute graft-versus-host disease; a post-transplant condition in which T-cells from the donor's bone marrow recognizes a recipient's body as foreign, and tries to attack.

"When regulatory T-cells don't respond to inflammation quickly enough to suppress an immune system response, the patient's own immune response can do considerable harm after a transplant, injuring organs, joints and other tissues of the body," said Dr. Bruce Blazar, senior author of the study and Director of the Clinical and Translational Science Institute at the U of M.

Compounding the challenge is that humans have a limited supply of regulatory T-cells, Blazar said. So even if the immune system's cells respond appropriately, there may not be enough suppressor cells to stop errant reactions in time before the immune response causes widespread tissue damage.

Researchers felt that by developing a way to replicate the cells—which have been historically challenging to coax into high rates of duplication—they could increase transplantation success rates.

Between 30-40 percent of all related bone marrow transplant patients experience graft-versus-host disease, and between 10-30 percent of kidney transplants and 60-80 percent of liver transplant recipients experience acute rejection, according to the National Institutes of Health.

About the New Method

The immunology team, led by Blazar, developed a method to extract regulatory T-cells from blood and subsequently deliver the right combination of signals to make the cells replicate up to 50 million fold. Previous methods to duplicate these cells led to only 70-fold expansion at best.

The findings are published in the May 18 edition of Science Translational Medicine.
"The ability to deliver such large quantities of these cells to patients before they undergo transplantation significantly reduces the chances of graft versus host disease and rejection of a transplanted organ," Blazar said.

In animal models and in human clinical trials (where smaller doses of regulatory T cells were given to patients), Blazar’s hypothesis came to fruition: Animals and patients became less likely to develop severe immune reactions that caused tissue damage.

The next step in Blazar’s work is phase 1 human clinical testing headed by the U of M’s Dr. John Wagner, a world renowned researcher who has been a leader in the field of blood and marrow transplantation. Wagner plans to lead a team of doctors who will administer increasing doses of regulatory T-cells before bone marrow transplants using Blazar’s new expansion method.

"This is truly exciting and a major, major breakthrough with profound implications in the treatment of our patients," Wagner said. "If we can super charge patients' immune systems before we do a transplant, we hope to eliminate the chance of graft-versus-host disease or rejection of the transplanted organ. Furthermore, we hope to move these trials ahead quickly to treat autoimmune diseases which affect hundreds of thousands of people worldwide."

Alongside Drs. Blazar and Wagner, U of M assistant professor Dr. Keli Hippen, the lead investigator of the study, pushed this new technology forward.

Collaborators from the University of Pennsylvania provided the key cell lines that made the research possible. Penn scientists engineered artificial Antigen Presenting Cells (aAPCs) which massively expanded regulatory T-cells. The process by which they were replicated could be used to generate a master cell bank that could be used to treat a large number of patients, making therapy much more feasible and cost effective.

Journal Reference:

Do Microbes Swim Faster or Slower in Elastic Fluids? Research Answers Long-Standing Question
ScienceDaily (May 18, 2011) — A biomechanical experiment conducted at the University of Pennsylvania School of Engineering and Applied Science has answered a long-standing theoretical question: Will microorganisms swim faster or slower in elastic fluids? For a prevalent type of swimming, undulation, the answer is "slower."

Paulo Arratia, assistant professor of mechanical engineering and applied mechanics, along with student Xiaoning Shen, conducted the experiment. Their findings were published in the journal Physical Review Letters.

Many animals, microorganisms and cells move by undulation, and they often do so through elastic fluids. From worms aerating wet soil to sperm racing toward an egg, swimming dynamics in elastic fluids is relevant to a number of facets of everyday life; however, decades of research in this area have been almost entirely theoretical or done with computer models. Only a few investigations involved live organisms.

"There have been qualitative observations of sperm cells, for example, where you put sperm in water and watch their tails, then put them in an elastic fluid and see how they swim differently," Arratia said. "But this difference has never been characterized, never put into numbers to quantify exactly how much elasticity affects the way they swim, is it faster or slower and why."

The main obstacle for quantitatively testing these theories with live organisms is developing an elastic fluid in which they can survive, behave normally and in which they can be effectively observed under a microscope.

Arratia and Shen experimented on the nematode C. elegans, building a swimming course for the millimeter-long worms. The researchers filmed them through a microscope while the creatures swam the course in many different liquids with different elasticity but the same viscosity.

Though the two liquid traits, elasticity and viscosity, sound like they are two sides of the same coin, they are actually independent of each other. Viscosity is a liquid's resistance to flowing; elasticity describes its tendency to resume its original shape after it has been deformed. All fluids have some level of viscosity, but certain liquids like saliva or mucus, under certain conditions, can act like a rubber band.
Increased viscosity would slow a swimming organism, but how one would fare with increased elasticity was an open question.

"The theorists had a lot of different predictions," Arratia said. "Some people said elasticity would make things go faster. Others said it would make things go slower. It was all over the map.

"We were the first ones to show that, with this animal, elasticity actually brings the speed and swimming efficiency down."

The reason the nematodes swam slower has to do with how viscosity and elasticity can influence each other.

"In order to make our fluids elastic, we put polymers in them," Arratia said. "DNA, for example, is a polymer. What we use is very similar to DNA, in that if you leave it alone it is coiled. But if you apply a force to it, the DNA or our polymer, will start to unravel.

"With each swimming stroke, the nematode stretches the polymer. And every time the polymers are stretched, the viscosity goes up. And as the viscosity goes up, it's more resistance to move through."

Beyond giving theorists and models a real-world benchmark to work from, Arratia and Shen's experiment opens the door for more live-organism experiments. There are still many un answered questions relating to swimming dynamics and elasticity.

"We can increase the elasticity and see if there is a mode in which speed goes up again. Once the fluid is strongly elastic, or closer to a solid, we want to see what happens," Arratia said. "Is there a point where it switches from swimming to crawling?"

**Journal Reference:**

**A New Wave of Hepatitis C**
*Boston Globe*, (05.16.2011) Chelsea Conaboy

On May 12, the US Department of Health and Human Services launched an action plan to prevent and treat viral hepatitis, calling it “a silent epidemic.” Some 3.5 million to 5.3 million Americans have viral hepatitis of some form, including up to 3.9 million with hepatitis C, and two-thirds of those infected are not aware of it, according to HHS.

“These infections have fueled a tragic cascade of human suffering,” said Howard K. Koh, MD, MPH, assistant secretary for health for HHS. “The new HHS action plan on viral hepatitis represents an unprecedented call to action for better education, treatment, and prevention.”

The Viral Hepatitis Action Plan seeks to boost the proportion of persons who are aware of their infection from 33 percent to 66 percent for hepatitis B virus and from 45 percent to 66 percent for hepatitis C virus. It also looks to reduce new HCV infections by 25 percent by 2020 and to eliminate mother-to-child HBV transmission.

Overall goals include raising awareness about viral hepatitis; expanding training to help health professionals diagnose, treat, and vaccinate people against viral hepatitis; and working within the health reform law to improve coverage of comprehensive prevention and treatment services.

Diagnosis and treatment of hepatitis C should be standard in drug treatment programs and correctional facilities, the plan says. It also recognizes the need for access to sterile syringe access programs and community health resources to help reduce stigma for patients infected by injection drug use.

“No one government agency can fight viral hepatitis alone, and here at CDC, we believe this action plan will not only strengthen the work we’ve been doing, but help all of us across the government collaborate to take our nation’s prevention efforts to the next level,” said CDC Director Thomas R. Frieden, MD, MPH.


**J&J Wins OK for First New AIDS Drug in 3 Years**
*Bloomberg News*, (05.20.2011) Alex Nussbaum

On Friday, Johnson & Johnson’s new HIV drug Edurant (rilpivirine) gained approval from the Food and Drug Administration. Taken once a day, Edurant is approved for use in combination with other antiretroviral drugs for treatment-naive HIV patients, FDA said. The non-nucleoside reverse transcriptase inhibitor, made by J&J’s Tibotec Pharmaceuticals unit in Ireland, is the first new HIV treatment licensed in three years.
In trials, Edurant was as effective as Sustiva (efavirenz) in lowering viral load when given in combination with other antiretroviral drugs. J&J will sell Edurant as a stand-alone pill for use in combination therapies, and it also has a planned combination pill with Gilead Science’s Truvada, which may be approved by FDA in August, Gilead COO John Milligan told investors this month.

"Patients may respond differently to various HIV drugs or experience varied side effects," said Dr. Edward Cox, director of the Office of Antimicrobial Products in FDA’s Center for Drug Evaluation and Research. “FDA’s approval of Edurant provides additional treatment options for patients who are starting HIV therapy.”

In a study released in July 2010, 9 percent of patients taking Edurant developed resistance, compared with 5 percent for efavirenz. "In the grand scheme of things, 9 percent is still pretty low," said Courtney Stanton, an analyst with Decision Resources Inc.

The most commonly reported side effects in those taking Edurant included depression, insomnia, headache, and rash. Fewer discontinued Edurant than efavirenz due to side effects, FDA said. For more information, visit: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm256087.htm.

China AIDS Sufferers Face Discrimination for Treatment—Study

A new report by the UN’s International Labor Organization finds that HIV/AIDS patients in China continue to be denied medical treatment in mainstream hospitals. ILO and China’s National Center for STD and AIDS Prevention Control said interviews with 103 people and 23 health care workers found widespread discrimination against HIV-positive patients.

At the press conference unveiling the report, one man recalled how he was denied treatment for back problems in hospitals in Tianjin and Beijing due to his HIV status. He was told that if he were treated, it would place other patients at risk. “I’ve visited many other hospitals and encountered similar denials and excuses such as a lack of equipment,” said the man, who added that he was forced to leave his job at a steel company after his boss learned he had HIV.

Another man, who contracted HIV through a blood transfusion, said workers at one hospital insisted on discharging him quickly after finding out he had the virus. “I talked to them later ... and their worry is that in rural hospitals, when an HIV-positive person receives procedures, very few people would visit the hospital,” he said. “They are worried about the impact on economic gains.”

People with HIV/AIDS are less likely to seek treatment as a result of persistent discrimination by health care workers, experts say. UN estimates show China had some 740,000 people living with the disease in 2009.

A key reason for HIV/AIDS discrimination by health care workers is China’s policy of treating those infected with the virus only in designated hospitals, said Zhang Ke, deputy director of the infectious-disease department at You An Hospital in Beijing. "We should eliminate these designated hospitals," Zhang said.

School Bullying Against LGBT Ups HIV Risk

The bullying of lesbian, gay, bisexual, and transgender youths at school is strongly linked to later health risks, including STDs and HIV, according to a new study.

The authors examined the association of LGBT school-based victimization and young adult psychosocial health and risk behavior. Data were based on a survey of 245 LGBT individuals ages 21–25, conducted by the Family Acceptance Project.

In the 10-item retrospective survey, respondents were asked to assess school bullying during ages 13-19. Multiple regression was used to test the association of bullying and young adult depression, suicidal ideation, life satisfaction, self-esteem, and social integration, controlled for background characteristics. Logistic regression was used to examine suicide attempts, clinical depression, heavy drinking and substance use, STD diagnoses, and self-reported HIV risk.

While there was no strong association with substance use or abuse, LGBT school victimization was strongly associated with later adult mental health problems and risk for STDs and HIV, reported lead author Stephen T. Russell, distinguished professor at the University of Arizona, and colleagues. Bullied LGBT youth later had lower self-esteem and life satisfaction and were more likely to have social adjustment problems, compared with less victimized peers.
“We now have evidence of the lasting personal and social cost of failing to make our schools safe for all students,” said Russell. “Prior studies have shown that school victimization of LGBT adolescents affects their health and mental health. In our study, we see the effects of school victimization up to a decade later or more. It is clear that there are public health costs to LGBT-based bullying over the long term.”

“The Family Acceptance Project’s growing body of research is building a solid foundation to develop preventive interventions to deal with the harmful effects of anti-LGBT environments on young people in their families, schools, and communities,” said Ann P. Haas, director of prevention projects for the American Foundation for Suicide Prevention.

Globalization exposes food supply to unsanitary practices
NEW ORLEANS, LA – May 23, 2011—As the United States continues to import increasingly more of its food from developing nations, we are putting ourselves at greater risk of foodborne disease as many of these countries do not have the same sanitary standards for production, especially in the case of seafood and fresh produce, say scientists today at the 111th General Meeting of the American Society for Microbiology in New Orleans.

"Approximately 15 percent of food consumed in the United States in 2006 was imported. Sanitation practices for food production are not universally equivalent throughout the world. Importing foods can move diseases from areas where they are indigenous to locations where they are seldom or do not exist," says Michael Doyle of the University of Georgia.

"The reality is we are going to continue to import foods at a greater rate in large part because labor costs in developing countries are much lower than they are here. We are going to see more food coming from developing countries which frequently have lower standards for producing foods," says Doyle.

In 2010 over 80% of fish and seafood consumed in the United States was imported, and much of that came from Asia. Raw domestic sewage and/or livestock manure are frequently used in fish farming in many Asian countries. In Thailand chicken coops (as many as 20,000 birds per farm) sit in rows suspended over ponds that hold shrimp and fish that feed on the waste that falls from above.

In China, crops and seafood are typically grown on small parcels where individual farmers try to produce as much food from their parcels as they can. To do that excessive amounts of pesticides for produce and antibiotics for fish and shrimp production are used. Many of these compounds are not approved for use in the United States. Untreated human waste and animal manure are often used to treat soils or aquaculture ponds.

Not surprisingly, contaminants found in imported foods are those primarily associated with fecal matter. Over one quarter of all contaminated seafood imports detained by the Food and Drug Administration (FDA) in 2001 were contaminated with Salmonella bacteria. More than half of those violations were shrimp.

Doyle warns that consumers should not immediately jump the gun and start avoiding foods from particular countries. Many U.S. companies import food and produce from these countries only if they can verify that the food was produced under stringent sanitary conditions.

"Just because it comes from a particular country that does not necessarily mean it is bad," says Doyle. Part of the problem is there is just so much coming into the country that the government can not inspect it all. The FDA physically inspects less than one percent of more than 10 million imported entries annually. But the onus should not be entirely on the government says Doyle.

"It is incumbent on food processors to ensure ingredients or products they import are produced under good sanitary practices. It is the industry that is responsible for producing safe foods. It is the government’s responsibility to verify that they are providing safe foods," says Doyle.

Comfort food: Probiotic-derived product protects in model of intestinal inflammation
Many people tout the beneficial effects of probiotics in preventing and/or treating several intestinal diseases, including ulcerative colitis. Although there have been few, if any, good clinical studies evaluating the clinical efficacy of probiotics, preclinical data suggest that probiotics and approaches utilizing probiotic-derived products could be effective therapies for acute and chronic gastrointestinal disorders. In this context, a team of researchers, led by Fang Yan, at Vanderbilt University Medical Center, Nashville, have now identified a new probiotic bacteria--derived soluble protein that can protect intestinal cells from inflammation and injury and unraveled its mechanism of action. Importantly, specific delivery of the protein (p40) to the colon provided therapeutic and prophylactic protection in several mouse models of
Mummies tell history of a 'modern' plague
Analysis of ancient Nubian-era mummies finds new evidence that disease spread from altering environment
Mummies from along the Nile are revealing how age-old irrigation techniques may have boosted the plaque of schistosomiasis, a water-borne parasitic disease that infects an estimated 200 million people today.

An analysis of the mummies from Nubia, a former kingdom that was located in present-day Sudan, provides details for the first time about the prevalence of the disease across populations in ancient times, and how human alteration of the environment during that era may have contributed to its spread.

The American Journal of Physical Anthropology is publishing the study, led by Emory graduate student Amber Campbell Hibbs, who recently received her PhD in anthropology.

About 25 percent of mummies in the study dated to about 1,500 years ago were found to have Schistosoma mansoni, a species of schistosomiasis associated with more modern-day irrigation techniques.

"Often in the case of prehistoric populations, we tend to assume that they were at the mercy of the environment, and that their circumstances were a given," says Campbell Hibbs. "Our study suggests that, just like people today, these ancient individuals were capable of altering the environment in ways that impacted their health."

The study was co-authored by Emory anthropologist George Armelagos; William Secor, an epidemiologist at the Centers for Disease Control and Prevention; and Dennis Van Gerven, an anthropologist at the University of Colorado at Boulder.

"We hope that understanding the impact of schistosomiasis in the past may help in finding ways to control what is one of the most prevalent parasitic diseases in the world today," Campbell Hibbs says.

Schistosomiasis is caused by parasitic worms that live in certain types of freshwater snails. The parasite can emerge from the snails to contaminate fresh water, and then infect humans whose skin comes in contact with the water.

Infection can cause anemia and chronic illness that impairs growth and cognitive development, damages organs, and increases the risk for other diseases. Along with malaria, schistosomiasis ranks among the most socio-economically damaging parasitic diseases in the world.

As far back as the 1920s, evidence of schistosomiasis was detected in mummies from the Nile River region, but only in recent years did the analysis of the antigens and antibodies of some of the individuals become possible.

This latest study tested desiccated tissue samples from two Nubian populations for S. mansoni. The Kulubnarti population lived about 1,200 years ago, during an era when Nile flooding was at its highest average known height, and archaeological evidence for irrigation is lacking. The Wadi Halfa population lived further south along the Nile, about 1,500 years ago, when the average heights of the river were lower. Archeological evidence indicates that the Wadi Halfa used canal irrigation to sustain multiple crops.

The analysis of tissue samples showed that 25 percent of the Wali Halfi population in the study were infected with S. mansoni, while only 9 percent of the Kulubnarti were infected.

The standing water collected by irrigation canals is particularly favorable to the type of snail that spreads the S. mansoni infection. Another form of the disease, Schistosoma haematobium, is spread by snails that prefer to live in more oxygenated, free-flowing water.

"Previously, it was generally assumed that in ancient populations schistosomiasis was primarily caused by S. haematobium, and that S. mansoni didn't become prevalent until Europeans appeared on the scene and introduced intensive irrigation schemes," Campbell Hibbs says. "That's a sort of Euro-centric view of what's going on in Africa, assuming that more advanced technology is needed to control the elements, and that irrigation conducted in a more traditional way doesn't have a big influence on the environment."

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Co-author George Armelagos is a bioarcheologist who has been studying ancient Nubian populations for more than three decades. Through extensive analysis, he and colleagues have shown that nearly 2,000 years ago the Nubians were regularly consuming tetracycline, most likely in their beer, at levels high enough to show they were deliberately brewing the antibiotic effects.

"The Nubians were probably in healthier shape than many other populations of their time, due to the dry climate, which would reduce their bacterial load, and because they were getting tetracycline," Armelagos says. "But the prevalence of schistosomiasis shown in this study suggests that their parasite load was probably quite heavy."

Mucus: Fighting the War Against Pollutants
ScienceDaily (Mar. 30, 2011) — Are our bodies vulnerable to some pollutants whose lack of solubility in water, or "hydrophobicity," has always been thought to protect us from them? New Tel Aviv University research has discovered that this is indeed the case.

Studies by Dr. Michael Gozin of Tel Aviv University's School of Chemistry at the Raymond and Beverly Sackler Faculty of Exact Sciences and Dr. Dan Peer of TAU’s Laboratory of Nanomedicine in the Department of Cell Research and Immunology have revealed that mucus—the thick substance lining those internal bodily organs that come into contact with the outer environment, such as the respiratory system, the digestive system, and the female reproductive system—may instead play an active role in the penetration of hydrophobic substances, including toxins and carcinogens, into our cells.

But encouragingly, the researchers believe that their discovery will one day prove useful in enabling non-water-soluble drugs to enter cells and treat diseases such as cancer. Their most recent study was published in the American Chemical Society's Chemical Research in Toxicology journal.

When mucus fails
Some of these dangerous substances, such as polycyclic aromatic hydrocarbons, are present in petroleum products and also formed through the partial combustion of fossil fuels that are used to operate power stations, planes, cars, space heaters, and stoves. In the new publication, Drs. Gozin and Peer describe their success in getting certain substances, some of them toxic, to penetrate digestive-system cell cultures and bacterial cells bathed in a mucus solution.

"Until now, mucus has been regarded as a mechanical and chemical protective membrane. We did not expect to find it actually absorbing these toxic hydrocarbons and facilitating their transport into bodily systems," explains Dr. Gozin.

Dr. Gozin, Dr. Peer and their research teams show that petroleum-based toxins can dissolve in water with the aid of mucins, the proteins that constitute the main component of mucus.

A new drug delivery system?
In their laboratory, Drs. Gozin and Peer bathed single-celled organisms in a solution of the hydrocarbon-mucin complex, and observed that the hydrocarbons penetrated the cells much more rapidly than when no mucins were present. "We do not know what mechanism enables these substances to penetrate the cell membranes. Clearly it is not a simple infiltration. Our assumption is that an endocytosis-like process is at work—substances are being absorbed into the cell through entrapment, with the cell membrane folding in on itself and creating a bubble," Dr. Gozin explains.

In an earlier study, published in 2010 in the nanotechnology journal Small, Dr. Gozin's team demonstrated that nanometer-scale substances such as carbon-based and inorganic fullerenes (ball-shaped nanoparticles) as well as carbon nanotubes can also be dispersed in physiological solutions with the aid of mucins.

"It will be possible to employ the mechanism we have discovered to facilitate the penetration of hydrophobic drugs into the body, whether via the respiratory tract—with drugs entering the body through the lungs—or by swallowing a delayed-release drug formulation to be absorbed by the digestive system beyond the stomach," Dr. Gozin notes. The next stage of the research will focus on developing systems for the transport of hydrophobic drugs.

Journal References:
US approval for hepatitis C drug telaprevir
Keith Alcorn
Published: 23 May 2011
The US Food and Drug Administration has approved a new hepatitis C drug telaprevir (Incivek), the agency announced today.

Telaprevir is a direct-acting antiviral drug (an HCV protease inhibitor), licensed for use in combination with the current standard treatment, pegylated interferon and ribavirin.

The drug has been developed by Vertex, which will market the drug in the United States.

Telaprevir is the second HCV protease inhibitor to be approved this month. The US Food and Drug Administration approved boceprevir (Victrelis) on 13 May.

The safety and effectiveness of telaprevir was evaluated in three phase 3 clinical trials with about 2250 adult patients who were previously untreated, or who had received prior therapy. In all studies, patients also received the drug with standard of care. In previously untreated patients, 79% of those receiving telaprevir experienced a sustained virologic response (i.e. the infection was no longer detected in the blood 24 weeks after stopping treatment), compared to standard treatment alone.

The sustained virologic response for patients treated with telaprevir across all studies, and across all patient groups, was between 20 and 45% higher than current standard of care.

The studies indicate that hepatitis C treatment can be shortened from 48 weeks to 24 weeks in most patients when telaprevir is used in the first 12 weeks. Sixty per cent of previously untreated patients achieved an early response and received only 24 weeks of treatment (compared to the standard of care of 48 weeks). The sustained virologic response for these patients was 90%.

Telaprevir is dosed as two pills taken three times a day with food. It should be taken in combination with pegylated interferon and ribavirin for the first 12 weeks. Most people with a good early response to the combination regimen at 12 weeks can be treated for 24 weeks rather than the recommended 48 weeks of treatment with the standard care.

The most commonly reported side-effects in patients receiving telaprevir in combination with pegylated interferon and ribavirin include rash, low red blood cell count (anaemia), nausea, fatigue, headache, diarrhea, itching (pruritus), and anal or rectal irritation and pain.

Rash can be serious and can require stopping Incivek or all three drugs in the treatment regimen. Telaprevir is expected to receive European Union marketing approval in the second half of 2011.

Second Drug Wins Approval for Treatment of Hepatitis C
On Monday, the Food and Drug Administration approved Vertex Pharmaceuticals’ Incivek (telaprevir), the second new hepatitis C treatment OK’d this month. Incivek is taken with traditional HCV drugs and is approved for treatment-naïve patients and those whose infection has not responded adequately to previous therapies, FDA said.

In clinical trials, 79 percent of patients taking Incivek-based combination therapy achieved a sustained virologic response. This SVR rate is between 20 percent and 45 percent higher than that achieved by patients taking traditional interferon and ribavirin therapy alone, FDA said.

About half of patients taking Incivek-based combination therapy were able to finish treatment in 24 weeks rather than the typical 48 weeks. Of treatment-naïve patients, 60 percent achieved an early response, received only 24 weeks of therapy, and had an overall SVR of 90 percent.

Incivek is taken three times a day (six pills total), and an entire course of treatment is $49,200 wholesale. Merck’s HCV drug approved earlier this month, Victrelis (boceprevir), costs $26,400-$48,400 depending on the duration of treatment. Both of the new HCV protease inhibitors are taken with standard treatment, which costs about $15,000-$30,000, depending on treatment duration.

The most commonly reported side effects in patients taking Incivek-based combination therapy were rash, anemia, nausea, fatigue, headache, diarrhea, itching, and anal or rectal irritation or pain. The rash can be severe enough to stop Incivek or all the drugs.

The new HCV drugs “represent a new direction in the treatment of hepatitis C and a significant improvement over the current standard of care,” said Dr. Margaret A. Hamburg, the commissioner of FDA.

Efforts to diagnose HCV are expected to get a boost, since many of the 3.2 million Americans with the virus are unaware of their infection. Vertex’s public awareness campaign may initially focus on New York City.
Africa: Putting MSM On the Radar
Khopotso Bodibe
23 May 2011
A three-day conference to be held in Cape Town from today will focus on men who have sex with men (MSM) as a key target group to consider in developing policy and interventions for HIV prevention and treatment.

Called Top to Bottom, the timing of the conference couldn't be more appropriate. It's just three weeks away from the 30th anniversary of the first-ever diagnosis of AIDS. In 1982, GRID or Gay Related Immune Deficiency was the first name proposed to describe what is known as AIDS today, as the condition was first seen among gay men in America. But soon after, the face of the epidemic changed from that of a gay man. It began to manifest in large numbers in general populations, with women becoming increasingly at risk. The condition was then renamed AIDS, Acquired Immune Deficiency Syndrome. The re-definition inadvertently led to the shift of focus away from gay men but with drastic consequences.

"There has been no government-focused MSM prevention campaign. You don't see bill-boards that talk about this. You don't see programmes that talk about this. It is very much a neglected population. I think that some of it is understandable. I think that we moved so rapidly into a generalised epidemic where women were particularly at risk that that's been the major focus. But I think MSM as a group have been neglected and have been left at very high risk and I think it's time to stop that" says Dr James McIntyre, Chief Executive Officer of Anova Health Institute, organizers of the conference.

But McIntyre believes that the government's attitude on men who have sex with men or the MSM community will soon change. He draws the inspiration from the fact that Health Minister, Dr Aaron Motsoaledi, has agreed to give the keynote address at the conference.

"That's indicative of the Department of Health and the Minister's personal response to MSM and recognising the need for programming. That's very, very positive", he says.

The winds of change are blowing. Perhaps even more encouraging is the response by the head of the South African National AIDS Council, Dr Nono Simelela, in a recent interview when asked what key issues the next National Strategic Plan on HIV and AIDS, which is currently being formulated, should address.

"Men who have sex with men, women who are in relationships with other women but also have sex with men" Simelela says.

"Those groups exist. Let's not pretend that those practices are not there. Let's talk about them. We've got a liberal Constitution. The Constitution says people are free to express. And if those groups need care and support, let's provide it. Let's get our health providers trained on dealing with those things and provide care in a rights-based manner: respect the dignity of people, respect the rights of people and provide them with care in the best possible way", she continues.

Anova's Dr James McIntyre says HIV infection levels among men who have sex with men are growing. A few studies suggest that more than 30% of men who have sex with men in some of the country's metropolitan areas are HIV-infected.

"Rates are a little higher than we see in heterosexual men. There have been rates of 33%, 40% in one study. In the Soweto men study in young gay men under the age of 25, the rates were very high. We were approaching 40%. They looked almost like the rate that you see in young women, whereas, in general, young men in South Africa have a much lower rate of HIV".

Some of the factors that drive the infection levels are peculiar to this community of men, and others are similar as in heterosexual relationships.

"What drives infection, very often, is unprotected anal intercourse and that in turn relates often to either the lack of condoms, not having lubrication, which is an important issue for men. The government does provide condoms, but doesn't provide lube. So, often people may use condoms but they will use it with oil-based lubricants where the condom may then develop holes and not work. There are issues around transactional sex as there are in the heterosexual community as well that is very often a survival tactic that we think drives it", McIntyre says.

But more research needs to be done to determine the risk factors.

"We are starting to investigate some research around violence within relationships and coerced sex that we don't know much about in this community at all. Men who have sex with men very often also have concurrent female partners. In one of the studies in Soweto of men who identified as having had sex with a man within the past year, 25% of them also had female partners. And so, we are not sure in this country of how much cross-over there is. Are these distinct epidemics or are these, in fact, epidemics that are
fuelling each other? Understanding that and tailoring messages that those men can relate to, that protect them in whatever their sexual choices becomes important”, he adds.

The conference is the first gathering of its kind to discuss sexual health issues affecting gay men or men who have sex with other men on the African continent.

**RWANDA: Trial of microbicide ring in final phase**

KIGALI, 23 May 2011 (PlusNews)—Rwanda is in the third and final phase of testing a vaginal ring containing antiretrovirals, which, if successful, could provide an important female-controlled method of HIV prevention.

Malawi, Rwanda, South Africa and Zimbabwe have all been selected to conduct the final phase of the trial. Phases I and II—conducted in Kenya, Malawi, Rwanda, South Africa—assessed the safety and acceptability of a daily application of a gel containing the ARV, dapivirine.

"Phases I and II were completed successfully; this means that the microbicide has been evaluated and found to be safe and acceptable," Gilles Ndayisaba, the principal investigator at Project Ubuzima, told IRIN/PlusNews. "Even if in Rwanda we conducted phase I and II on the gel, these phases have been done with the ring in several others [countries] and they were successful," he added.

Phase I trials involved small numbers of women, followed by expanded safety trials, Phase I/II, which gathered additional safety data among more participants over longer periods. Once the safety trials are complete, longer-term safety and efficacy trials begin. Phase III trials are conducted among high-risk participants so that researchers can see if there is a difference in infection rates between women who use the active microbicide product versus those who use a placebo. This phase looks specifically at the efficacy and gathers information to proceed with putting the product on the general market.

In Rwanda, the trials are being conducted by a local NGO, Project Ubuzima, with the International Partnership for Microbicides. The project has carried out safety trials for dapivirine gel among more than 60 women and has conducted an HIV incidence study among 1,250 female VCT clients and 800 high-risk women in the capital, Kigali, in preparation for the final phase.

An estimated 3,000 HIV-negative women aged between 18 and 40 will participate in the trial in all selected countries—between 400 and 600 will come from Rwanda; the trial is expected to last three years. "Potential participants are well-educated on clinical research in general and first have to sign an informed consent form which includes all information concerning risks and benefits while participating in the study," said Marie-Michelle Umulisa, the community outreach manager at Project Ubuzima. "These are reviewed by the Rwandan National Ethics Committee to protect participants' rights."

Each participant will use the ring for a minimum 15 months or a maximum 33 months. "It is likely that products that can be applied less frequently like the ring will be more acceptable and will achieve better adherence," Ndayisaba said. "Vaginal rings need only to be replaced every four weeks and may therefore have benefits over dosage forms that need to be used more frequently."

The researchers say dapivirine is advantageous because it is not used in current HIV/AIDS treatment regimens so there is less potential for drug resistance. They say the vaginal ring is cheap to manufacture, comfortable, flexible and can be self-inserted; it is intended to provide long-term protection during anticipated and unanticipated sexual intercourse.

**Uncertainties**

According to Evelyn Kestelyn, executive director of Project Ubuzima, there are advantages to being one of the countries conducting a trial. "When the products finally come on the market... countries that were selected to implement phase III will get the products for free or will purchase them at a subsidized price."

However, women in Kigali remain uncertain about whether they would use a microbicide ring should the ongoing trial prove successful.

"I would need to be extremely sure it works well before I can entrust my life with such a thing; I mean I would want to be sure it doesn’t have any particular side-effects," said Agatha Ingabire.

Should the product make it on to the market, Project Ubuzima plans a major campaign to sensitize Rwandans on the microbicide’s function.
"We intend to undertake a huge sensitization process, starting with community leaders and gradually we shall trickle this down to the other masses," said Umulisa. "Community acceptability of this project is key for its success."

Globally, a number of microbicide trials are ongoing, testing gels and rings. In 2010, the biggest success was recorded in a study by the Centre for the AIDS Programme of Research in South Africa, which found that a vaginal gel containing the ARV tenofovir was 39 percent effective in reducing a woman's HIV risk when used for about three-quarters of sex acts and 54 percent effective when used more consistently.

'Don't Say Gay' Bill Clears State Senate

The Tennessean (Nashville), (05.21.2011) Chas Sisk

The Senate voted 20-10 on Friday in favor of a bill that prohibits discussion of homosexuality in elementary and middle school classes. Its opponents, who have dubbed the measure the "Don’t Say Gay" bill, say it confuses state law, which already bans all sex education until high school.

"We have been steadfast in our desire to say that we should not have age-inappropriate material in K through eight," said Sen. Andy Berke (D-Chattanooga). "What we’re doing here is passing something just to pass it.” In the state House, companion legislation did not advance out of committee; supporters have no plans to bring it up again until next year.

But Sen. Stacey Campfield (R-Knoxville), who has pushed the measure for several years, believes it is needed to ensure that homosexuality is not discussed until high school. The bill attracted nationwide attention and drew student protestors to the Capitol, including 13 youths who were on hand Friday.

The vote to approve SB 49 came after it was amended to ban discussion of gays and lesbians only in prepared materials and instruction—meaning teachers would be able to respond to questions about homosexuality without facing punishment.

"Teachers could respond to that, but they couldn’t be offering materials,” Campfield said. “They couldn’t say, ‘Today, we’re going to teach about homosexuality, lesbianism.’ That can’t be part of the course work.”

Breastfeeding OK for Moms with Hepatitis B: Study

Reuters, (05.05.2011) Genevra Pittman

A new study shows that new mothers infected with the blood-borne hepatitis B virus (HBV) can safely breastfeed their babies, provided proper immunoprophylaxis methods are taken.

Dr. Zhongjie Shi, of Philadelphia’s Temple University, and colleagues conducted a systematic review of prospective studies to clarify the role of breastfeeding in mother-to-child HBV transmission. Data from 10 studies, all conducted in China, compared HBV rates in the babies of more than 1,000 mothers with the virus; about half these women breastfed their babies.

To prevent hepatitis B transmission, babies are vaccinated against HBV at birth and given another injected medicine soon after birth. Infants also are vaccinated two or three more times during the first few months of life.

The review showed that by their first birthday, 31 babies out of the 637 with breastfeeding mothers were HBV-positive. By comparison, 33 babies of 706 mothers who did not breastfeed became infected. Most of the infected infants had contracted HBV during pregnancy or childbirth, the researchers noted.

Blood is the primary vector for mother-to-child transmission, followed by amniotic fluid and vaginal secretions, said Shi.

Even in HBV-infected mothers, "breastfeeding should be recommended as a valuable source of nutrition to infants,” said Shi. However, mothers should avoid the practice if they have cracked or bleeding nipples or lesions on their breasts, since this could transmit the virus more easily, the researchers said.

According to Shi, the study results "are most valuable in developing countries and areas with high [HBV] prevalence or heavy population, such as India, China, [and] southeast Asia."

Circumcision Ban to Appear on San Francisco Ballot
Associated Press, (05.19.2011) Robin Hindery
San Francisco election officials recently confirmed that a citizens’ initiative to ban male circumcision in the city will be placed on the November ballot. The initiative garnered more than 7,700 valid signatures from city residents, more than the 7,168 it required.

If approved, the ban would prohibit circumcising males under the age of 18 and carry a misdemeanor penalty of up to $1,000 or up to one year in jail. There are no religious exemptions, prompting widespread criticism that it would violate First Amendment freedoms to exercise one’s religion.

Male circumcision is seen as a sacred rite by Jews and Muslims. Activists behind the city ballot initiative regard the procedure as genital mutilation, similar to that forbidden for girls, as well as a painful, dangerous procedure forced on a child.

“Parents are really guardians, and guardians have to do what’s in the best interest of the child,” said Lloyd Schofield, the proposal’s lead advocate. “It’s his body. It’s his choice.”

“For a city that’s renowned for being progressive and open-minded, to even have to consider such an intolerant proposition ... it sets a dangerous precedent for all cities and states,” said Rabbi Gil Yosef Leeds of Berkeley, a mohel, or one who performs Jewish ritual circumcisions.

The World Health Organization recommends male circumcision to prevent HIV in countries with generalized heterosexual HIV epidemics. Male circumcision has proven to reduce the risk of female-to-male HIV transmission by up to 60 percent in several randomized controlled trials in Africa. However, studies have not shown circumcision to prevent HIV transmission among men who have sex with men.

US health officials are still developing recommendations regarding male circumcision. CDC does not have a position on the ballot initiative, said agency spokesperson Elizabeth-Ann Chandler.

Defense Troops at Risk of HIV from Iraq
Australian Associated Press, (05.24.2011)
At the Australian Defense Force’s main hospital unit in the Middle East, failure to properly sterilize surgical equipment may have exposed soldiers and contractors stationed in Iraq to blood-borne diseases including HIV and hepatitis, according to a Fairfax newspapers report. The breach occurred at the al-Minhad air base in the United Arab Emirates from February 2009 to August 2010; however, personnel were informed only last week. ADF’s memo says the risk of infection is low, particularly given that force members received hepatitis vaccinations. Measures have since been put in place to prevent such errors in the future, wrote Major General P.V. Alexander, ADF’s surgeon-general.

Doctors Report Hundreds Of New Cholera Cases In Dominican Republic
A cholera outbreak in the Dominican Republic appears to be spreading, and health officials are reporting hundreds of new cases, the Associated Press/Washington Post reports. "Deputy Health Minister Jose Rodriguez says there have been 1,143 cases of cholera and 14 deaths since the outbreak began in November. The number of new cases reported Monday is up about 50 percent since the middle of May," the news service writes (5/23).

According to the physicians’ union in the Dominican Republic, cases of cholera have been confirmed in 28 of the country’s 32 provinces, FOX News Latino reports (5/23).

Pandemic influenza H1N1 in Mexico
Gerardo Chowell and coworkers report the incidence of pandemic influenza H1N1 morbidity and mortality in 32 Mexican states in 2009 and quantify the association between local influenza transmission rates, school cycles, and demographic factors. By using the epidemiological surveillance system of the Mexican Institute for Social Security, which covers about 40% of the Mexican population (107 million individuals), they compiled age- and state-specific rates of incident influenza-like illness and pandemic H1N1 influenza cases by day of symptom onset to analyze the geographic patterns of the dissemination of the flu pandemic across Mexico in 2009. Using these data as inputs to a mathematical model they show that the age distribution of pandemic influenza morbidity was greater in younger age groups while the risk of severe disease was highest in older age groups. But most importantly, these findings support the effectiveness of early mitigation efforts including mandatory school closures and cancellation of large public gatherings, reinforcing the importance of school cycles in the transmission of pandemic influenza.
No superinfections among HIV-positive gay men in Amsterdam reporting risky sex
Michael Carter
Published: 25 May 2011

HIV superinfection appears to be extremely rare, a Dutch study published in the June 1st edition of the Journal of Infectious Diseases suggests.

The study is one of the few attempts to use ongoing virological monitoring and behavioural data to establish the likely incidence of superinfection, albeit in a small cohort, and points to the neglect of a question that remains important for giving advice on HIV prevention strategies that might encourage the practice of serosorting—sex, most likely unprotected, with partners of the same HIV status.

Researchers monitored 15 HIV-positive gay men for evidence of superinfection for an average of almost six years. All the men either reported unprotected anal sex, or had a history of sexually transmitted infections. Despite this risk, no cases of superinfection were detected.

"With no putative case of HIV-1 superinfection detected in 15 individuals over a total of 88.3 PY [per years], we observed a low incidence rate of HIV-1 superinfection (incidence rate: 0 per 100 PY, 95% CI: 0.42)," write the investigators.

However, they do not regard their results as definitive and call for further research into this matter. In particular, they speculate that the level of risk of the men in their study may not have been high enough to lead to superinfection.

Intensive case finding has identified approximately 50 cases of confirmed HIV superinfection (infection with a second strain of the virus).

Some investigators have speculated that the phenomenon may be much more common than this figure suggests.

To try and establish a better understanding of this controversial subject, investigators from the Netherlands studied blood samples obtained from 15 HIV-positive gay men recruited to the Amsterdam Cohort Study between 1986 and 1997.

Blood samples were obtained from these men every three months, and at six-monthly intervals they were interviewed about their sexual behaviour. All the men reported unprotected anal sex with at least two partners in one or more six-month period, and/or infection with syphilis or gonorrhoea.

Phylogenetic analysis was used to see if any of the men had been superinfected with another strain of HIV.

Of note, the study was conducted using samples obtained in the era before effective antiretroviral therapy became available. Superinfection among individuals treated with HIV therapy appears to be extremely rare.

A total of five individuals reported four six-month periods of risk; five patients reported three periods of risk; and the remaining five individuals reported one or two risk periods.

Overall, the men contributed over 88 person years of follow-up, an average of 5.8 years per patient. Intensive phylogenetic analysis failed to detect a single case of superinfection.

"While we had expected to increase the odds of detecting HIV-1 superinfection in this study by studying longitudinal samples covering time periods of unsafe sexual risk behaviour, no cases of superinfection were detected," write the authors.

However, they note that they may not have been able to detect minority populations of superinfecting virus, or transient superinfection.

Even though the patients enrolled in their study reported risky sex, the investigators suggest that this may not have been at a sufficient level to lead to superinfection. They note that HIV-positive African sex workers who were superinfected reported “a 10-fold to 30-fold higher number of sexual partners than homosexual men in our cohort.”

The investigators conclude that their analysis “resulted in absent detection of HIV-1 superinfection and hence a low incidence of HIV-1 superinfection in this study may point to external risk and/or host factors involved in acquisition of HIV-1 superinfection.”

They suggest that “additional longitudinal studies are needed to estimate the impact of each factor that may increase the risk for establish of HIV-superinfection.”

However, conducting such studies may be difficult in settings where men could be criminalised either for HIV transmission or for non-disclosure of HIV status. Men may be disinclined to provide frank information about their sexual behaviour in such settings, even where the object of inquiry is sex with partners of the same HIV status.
30 years of AIDS – An interview with Helen Epstein
By John Donnelly  · May 24, 2011

Freelance writer and independent public health consultant Helen Epstein.

How did you first get involved in writing about AIDS?
I was working as a molecular biology post-doctoral fellow at the University of California-Davis in the early 1990s and I began to think about how I wanted to spend the rest of my life. I was fascinated by biology and science, but I also was fascinated by people. I had friends who had died of AIDS, and I knew the epidemic was really raging in Africa. I wanted to apply all I had learned as a biologist to the problem. In those days, there was far less research going on in Africa than there is today. But I heard about a team from the University of California-San Francisco working at Mulago Hospital in Kampala, Uganda. I joined them as an unpaid volunteer to set up experiments to explore the serotypes, the different types of HIV circulating, for a vaccine study. When I got there I realized that developing a vaccine was going to be very, very complex. Nonetheless, I became fascinated by the problem of HIV, and I kept working on it for the next two decades.

What was your first story?
It was a memoir of working on that vaccine project for Granta magazine in 1995.

What do you remember about the story?
What I tried to do was tell my own personal story, within the larger quest for an AIDS vaccine for Uganda and the world. I wanted to use that to tell a larger story about the country, and why the AIDS crisis was so severe at that time. One of the themes that came out of that piece, and stayed with me, is the disconnect between the good intentions of people who go out there to help and the realities of the problems in those countries.

Why was there a disconnect?
We have enough difficulty trying to solve our own problems here in the U.S. Problems in other countries are the product of so many things – their culture, economy, relationships with the rest of the world. It’s hard to imagine a group of Ugandans could come here and solve the problems in our health care system, or with our economy, after all. You can see why so many of our efforts backfire, and don’t work as well as they might. We tend to over-theorize things rather than really listen to the people in these countries.
Over the course of the epidemic, what stands out as a moment that was most important to you personally?
That’s easy. I had written a few articles about AIDS, and at the time, publishers were keen to have a book written about AIDS in Africa. I got a contract, but at first it was very hard for me to see the big picture, to understand what was going on. There was this critical moment, an intense email exchange with a group of researchers, including Daniel Halperin, Rand Stoneburner, Vinand Nantulya, and Edward Green. It was about what had happened in Uganda, and why HIV rates had fallen by about 60 percent there during the early 1990s. This was quite remarkable. I had been living in the country at the time, but the results only came out years later, and I had not thought about them much; I had assumed it was a combination of general behavior change, and condom use, and other things. That’s what journal articles had suggested.

But according to these researchers, it was actually partner reduction that played the major role and condoms played a minor role. Daniel and Rand had independently re-analyzed a set of important sexual behavior surveys from the late 1980s and early 1990s, and this is what they found. This contradicted earlier analyses of those same surveys, which suggested increased condom use was the major cause of the decline. Later on I teamed up with an economist at Princeton and reproduced their finding. This raised an important paradox. Surveys showed that Africans didn’t have more sexual partners over a lifetime than heterosexual people in the West – some surveys suggested they had fewer. What was fueling the AIDS crisis in the gay community in the U.S. was clear: a lot of partner change. One hundred partners a year was not unusual in the gay community in the early 1980s. But this seemed not to be the case in Africa. So what was going on?

I was speaking to some other researchers who had recently seen a presentation by Martina Morris at the University of Washington on her theory concerning concurrent sex partners. It wasn’t only the number of sexual partners that was driving the epidemic, but also the degree to which sexual partners formed a network of overlapping long term relationships. If true, it would resolve this extraordinary paradox, and explain why partner reduction had such a powerful effect on the HIV rate in Uganda, and condom use had a relatively low effect. I later went back to various countries, including Botswana and South Africa, and interviewed ordinary people, who were identified through HIV support groups, and other organizations, and were willing to talk about their lives, and about patterns of sexual behavior in their communities. It was a casual process, not systematic, but what they told me did support the concurrency theory. When I discussed the theory with them, it was like a light went on in their heads. This includes senior health officials in some African governments. They were struck by the theory. That became the theme of my book.

Many journalists say that so much has been written about AIDS that they, and their editors, are fatigued. What’s important to cover now?
For me, as far as AIDS goes, the most important thing now is to really evaluate and test the concurrency hypothesis, because it has crucial implications for HIV prevention programs. The people most likely to do that are the scientists, policymakers, and so on, and they are not going to be influenced by journalists at this point, but they might be influenced by peer-reviewed articles.

In addition, it would be great if Africans themselves wrote more about AIDS in their own countries. Most of the stories I read in African newspapers now tend to be from a distance, citing statistics, reporting on some expert’s speech, but not the kind of really deep, descriptive writing such as that of say, Johnny Steinberg (a South African author).

During the AIDS crisis in the U.S., in the 1980s, the predominately white gay community responded in so many creative ways to this problem. So many people were writing poems, essays, plays about AIDS. When I was in Uganda in the early 1990s, I saw the same thing, if in an African way – candlelight vigils, all day meetings, murals, plays. I think it is no coincidence that Uganda’s HIV infection rate was falling at the time, just as it was in the U.S. But this deeper cultural response has been largely absent in other African countries. This silence is unfortunate.

The same thing could be said about African American communities today; there’s a staggeringly high HIV rate, but a terrible silence around AIDS. There’s no way an outsider can motivate behavior change if people themselves don’t want to talk about it. No technical inputs – drugs, condoms, HIV tests, etc. – will have much effect on the number of people who become infected. These things will alleviate some of the suffering, but the path of the epidemic won’t change without a broader internal, cultural response.
US Objects to New Law on Clinics in Indiana


An Indiana law that steers money away from health care providers whose services include abortion may violate federal statutes. The new law exempts hospitals, but affects Planned Parenthood of Indiana. Of the 85,000 patients PPI served last year, 9,300 were in the federal- and state-funded Medicaid program. Most received contraceptives, but PPI also provided 26,500 Pap smears and 33,000 STD tests last year.

Federal officials have 90 days to review the law, which took effect on May 10. Administration officials have signaled they will not approve certain changes affecting Medicaid. If a state’s program is out of compliance, federal officials can take corrective action including “the total or partial withholding” of federal Medicaid funds. Administration officials say the law impermissibly restricts the recipients’ choice of health care providers.

“Federal law prohibits federal Medicaid dollars from being spent on abortion services,” the Centers for Medicare and Medicaid Services noted in a statement on the law. “Medicaid does not allow states to stop beneficiaries from getting care they need, like cancer screenings and preventive care, because their provider offers certain other services. We are reviewing this particular situation and situations in other states.”

Kansas Gov. Sam Brownback is expected to sign a similar bill. Other states that have considered restricting payments to Planned Parenthood include North Carolina, Oklahoma, Texas, and Wisconsin.

The Indiana law prohibits state agencies from awarding grants to or contracting with “any entity that performs abortions or maintains or operates” a facility that does so. Of Indiana Medicaid funds, about 66 percent are federal dollars, jumping to 90 percent for family planning.

“Medicaid clients who went to Planned Parenthood will have to go to someone else,” said Marcus J. Barlow, a spokesperson for Indiana Family and Social Services Administration. “This is not a change in services. It’s a change in providers.”

Shorter Treatment More Effective for Latent TB

SUMMARY

Rifapentine plus isoniazid administered once-weekly for 3 months to treat latent tuberculosis worked better than daily isoniazid for 9 months, with fewer premature treatment discontinuations, researchers reported at the recent American Thoracic Society meeting.

Below is an edited excerpt from a press release issued by the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP) describing the study and its results. Additional research will be needed to determine if these findings also apply to people with HIV and to individuals in high TB prevalence countries.

Research Offers Simpler, Effective Treatment Option for Latent TB Infection

May 16, 2011—Results from one of the largest U.S. government clinical trials on tuberculosis preventive therapy to date suggest that treatment for latent tuberculosis (TB) infection—normally a difficult and lengthy regimen—may soon be easier than ever before in countries with low-to-medium incidence of TB. The trial results showed that a supervised once-weekly regimen of rifapentine and isoniazid taken for three months was just as effective as the standard self-administered nine-month daily regimen of isoniazid, and was completed by more participants.

The multi-country, CDC-sponsored trial tested the effectiveness of this new preventive TB treatment regimen (using currently available anti-TB drugs) among persons with latent TB infection who are at high risk for progression to TB disease. The results were presented today at the American Thoracic Society International Conference in Denver by principal investigator Timothy Sterling, MD, of Vanderbilt University.

"Although the standard regimen is very effective in treating latent TB infection, ensuring that those who need treatment both begin and complete the lengthy, cumbersome isoniazid regimen is challenging," said CDC Director Thomas R. Frieden, MD. "New, simpler ways to prevent TB disease are urgently needed, and this breakthrough represents one of the biggest developments in TB treatment in decades."

Latent TB infection occurs when a person has TB bacteria in his or her body, but does not have symptoms and cannot transmit the bacteria to others. However, if the bacteria become active, the person will develop TB disease, become sick, and may spread the disease to others. Although not everyone with latent TB infection will develop TB disease, some people, such as those with weakened immune systems, are at higher risk of progression to TB disease.
The new regimen to treat latent TB reduces the doses required for treatment from 270 daily doses to 12 once-weekly doses, making it much easier for patients to take.

In the United States, the number of persons with TB disease is at an all-time low (11,181 total cases were reported in 2010); however, approximately 4 percent of the U.S. population, or 11 million people, are infected with the TB bacterium. TB continues to disproportionately affect racial/ethnic minorities and foreign-born individuals in this country.

"If we are to achieve TB elimination in the United States, we must address the large number of people in this country with latent TB infection," said Kevin Fenton, MD, director of CDC’s National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention. "By effectively treating latent TB infection, not only can we reduce the potentially deadly consequences among those individuals, but we can also prevent many others from ever becoming infected."

**One of the largest TB prevention trials to date**

The study lasted approximately 10 years and included 8,053 participants over the age of 2 who lived in countries with low or medium TB incidence, with the majority from the United States or Canada. Additional participants were located in Brazil and Spain. Because of a known drug interaction between some anti-HIV drugs and rifapentine, HIV-infected persons taking antiretrovirals were not eligible for enrollment in the study.

Participants were randomized to receive one of two preventive treatment options—a regimen consisting of three months of once-weekly rifapentine 900 milligrams and isoniazid 900 milligrams given with supervision (that is, directly observed therapy), or the current standard regimen used to treat latent TB infection, consisting of nine months of daily isoniazid 300 milligrams, which was not supervised (that is, self-administered by the participant). Each participant was evaluated for treatment-related adverse events, adherence to treatment, survival, and development of TB disease for a total of 33 months after the date of their enrollment.

The new regimen was found to be safe and as effective as the standard regimen in preventing new cases of TB disease, with very few cases of TB disease developing in either study arm. Seven cases occurred among those receiving the new treatment regimen compared to 15 among those receiving the standard treatment. Additionally, the percentage of participants completing the new, shorter regimen was substantially higher (82 percent) than the percentage completing the standard regimen (69 percent).

**Next steps in implementation**

Given the promise of these results, CDC has already held an expert consultation to review the data and begin working on new guidelines for its use in the United States. Researchers caution that these results are only directly applicable to countries with low-to-medium incidence of TB. Additional studies will likely be needed before this new regimen can be recommended in countries with a high incidence of TB, especially those with high HIV prevalence and where the risk of TB re-infection is greater.

The research was conducted through the TB Trials Consortium (TBTC), a CDC-funded partnership of domestic and international clinical investigators who conduct research on the prevention and treatment of TB. 5/20/11

**Reference**


**World Health Assembly Delays Destruction Of Smallpox Reserves For Three Years**

Following "two days of heated debate," representatives meeting at the World Health Assembly in Geneva decided to delay for three years the destruction of smallpox virus reserves held by the U.S. and Russia, rejecting a U.S. plan that would have delayed the action for five years, the Associated Press reports (5/24).

The U.S. and Russia led the campaign to keep virus stocks, while Iran headed up a group of nations looking to eliminate reserves of the disease, which was eradicated more than three decades ago, according to Reuters (Lewis, 5/24). "Since then, there has been a debate between so-called destructionists, who argue that the world will be safer with the last virus gone, and so-called retentionists, who argue that more research on vaccines, therapies, and diagnostics is needed because bioterrorists might one day get their hands on hidden stashes of the virus," Science’s "ScienceInsider" writes (Enserink, 5/24).

Reuters also reports that the WHA passed “28 resolutions and three decisions on guiding future work” (5/24). They included statements on strengthening health systems, preventing non-communicable diseases, eradicating polio and improving access to water and sanitation, according to a WHO press release (5/24).
Nature reports on a WHO reform proposal approved last week at the WHA meeting and how the agency may move forward to "bring the biggest changes to the agency in its 63-year history" (Butler, 5/24).

**Vatican Newspaper Article Addresses Condom Use Among Married Couples**

Three days before the start of a Vatican conference focusing on "the centrality of care" in HIV/AIDS prevention and treatment, the Vatican's official newspaper, L'Osservatore Romano, on Tuesday printed a piece by Spanish theologian Juan Jose Perez-Soba arguing that married couples with one HIV-positive partner "should abstain from sex, because intercourse performed with a condom is, 'from the moral point of view, not a fully conjugal act'," RNS/Beliefnet News reports (Rocca, 5/24).

Perez-Soba "said that although use of a condom may have some effectiveness against HIV/AIDS contagion in single acts, it cannot guarantee safety – especially throughout the sexual life of a couple. It is wrong, therefore, to say that condom use can prevent infection, he said," according to the Catholic News Service. CNS writes that Perez-Soba's article "said that, on a practical level, condom campaigns increase the possibility of AIDS infection by promoting a false sense of security" (Thavis, 5/24).

Last year, Pope Benedict XVI addressed condom use for HIV prevention in an interview published in November 2010 that "touched off worldwide controversy. ... The Vatican's doctrinal office later insisted that the pope's words did not mark a change in Catholic moral teaching or 'pastoral practice' against the use of condoms for AIDS prevention or contraception," according to RNS/Beliefnet News (5/24).

**Long-term study of swine flu viruses shows increasing viral diversity**

DURHAM, NC and SINGAPORE – Increased transportation of live pigs appears to have driven an increase in the diversity of swine influenza viruses found in the animals in Hong Kong over the last three decades, according to a new study.

In the longest study of its kind, Duke-NUS Graduate Medical School researchers found that swine viruses crossed geographic borders and mixed with local viruses, increasing their diversity.

"The majority of reported human infections have been people with close contact to farm animals," said Vijaykrishna Dhanasekaran, Ph.D., an assistant professor at Duke-NUS, who works in the Laboratory of Virus Evolution.

"I think the risk of swine-to-human transmission has not increased greatly, but the diversity of swine viruses has increased as shown in our study," Vijaykrishna said. "This means that the repertoire of viruses that humans are in contact with everyday has increased and this may lead to a higher likelihood of swine-to-human transmission, although the risk remains unquantified."

The study was published online in the journal Nature on May 25.

"The geographic transport of swine viruses that we highlight in our study is likely through the transport of live pigs," Vijaykrishna said. "Most swine viruses that have been described to date have been isolated from farmed pigs in Asia, Europe and North America. Some viruses have been isolated from backyard pigs in southeast Asia. However, no information is available on status of influenza in naturally roaming wild or domestic pigs."

The study looked at the epidemiology, genetics and antigenic properties of swine influenza virus in Hong Kong from more than 650 samples taken from swine, more than 800 swine blood specimens from 12 years of surveillance, and 34 years worth of other data on swine flu viruses. Antigens are the features on the surface of the virus that pigs and humans develop antibodies against to fight the infection. Influenza viruses evade the immune response by mutations in the hemagglutinin protein, an attachment protein that serves as an antigen. Antibodies formed during previous infections fail to recognize the newly mutated antigen, which is why seasonal influenza vaccines have to be reformulated each year.

Mutations in the swine influenza hemagglutinin have been linked to reassortment, which is the mixing of genetic material from multiple virus species into new combinations, said Vijaykrishna. The greater viral diversity they found in the swine flu viruses may mean more possible combinations from reassortment.

"These results provide important clues into the mechanism of influenza virus evolution in general," he said.

The researchers discovered that two major lineages of H1 subtype viruses and the human H3N2 viruses were frequently detected in swine. Several combinations of the three lineages were detected in pigs, including some avian (bird) viruses.
While the pigs had no symptoms or very mild undetected symptoms to most viruses isolated for the study, the scientists don’t know how virulent these viruses can be in humans. “It is important to monitor viruses in swine, especially those that can emerge in humans that we do not have antibodies for,” said Vijaykrishna, who is a faculty member of the Duke-NUS Program on Emerging Infectious Diseases.

**Immune System Release Valve**

*Weizmann Institute scientists reveal a new mechanism for keeping inflammation in check*

The molecular machines that defend our body against infection don’t Huff and puff, but some of them apparently operate on the same principle as a steam engine. Weizmann Institute scientists have discovered a mechanism that controls inflammation similarly to a steam-engine valve: Just when the inflammatory mechanism that protects cells against viruses reaches its peak of activity, the molecular “steam-release valve” interferes, restoring this mechanism to its resting state, ready for re-activation. This finding might shed new light on such inflammatory disorders as rheumatoid arthritis or inflammatory bowel disease, and point the way to developing effective therapies.

How does the cellular “steam-release valve” work? The scientists have discovered that its crucial component is the enzyme called caspase-8. When the cell is invaded by a virus, caspase-8 joins a large molecular complex that forms in order to send out an inflammatory signal. However, this same signal, once triggered, makes sure that the inflammatory response will eventually be shut down. The mechanism can be likened to the peak of the steam cycle when the valve opens, releasing steam and restoring the engine to its initial position. In the case of the cell, the inflammatory signal prompts caspase-8 to destroy a protein called RIP1 – a crucial signal amplifier – after RIP1 has reached a state in which it can produce maximal amplification. The inflammatory cycle is thus completed: The signaling mechanism, precisely after reaching its peak activity level, returns to its neutral state, ready to enter yet another inflammatory cycle in case the cell is still under viral attack.

Until recently, caspase-8, discovered by study leader Prof. David Wallach of Weizmann’s Biological Chemistry Department some 15 years ago, was known to prevent inflammation in only one way – by causing damaged cells to self-destruct in a process called apoptosis. In the course of this process, the contents of the dying cells are prevented from spreading around and triggering inflammation. The present study, reported recently in *Immunity*, reveals an entirely new mechanism by which caspase-8 can control inflammation more directly. The research was performed in Wallach’s lab by Dr. Akhil Rajput, Dr. Andrew Kovalenko, Dr. Konstantin Bogdanov, Seung-Hoon Yang, Dr. Tae-Bong Kang, Dr. Jin-Chul Kim and Dr. Jianfang Du.

The study results might be relevant for various types of inflammation – not only that caused by viruses – and can thus provide important insights into inflammatory disorders. Since such disorders may occur when the inflammatory response fails to be shut down properly, it’s possible that caspase-8 malfunction and the resulting excessive activity of the RIP1 “signal amplifier” might be involved. And if this is indeed the case, a new treatment approach could aim at blocking RIP1, thereby fighting inflammation in a precise and selective manner.

**Educational Effectiveness of an HIV Pretest Video for Adolescents: A Randomized Controlled Trial**

*Pediatrics Vol. 127; No. 5; P. 911-916*, (05..2011)  Yvette Calderon, MD, MS; Ethan Cowan, MD, MS; Jillian Nickerson, BA; Sheba Matthew, MD; Jade Fettig, MS; Michael Rosenberg, MD, PhD; Christopher Brusalis, BA; Katherine Chou, MD, MS; Jason Leider, MD, PhD; Laurie Bauman, PhD

The authors compared the effectiveness of a youth-friendly HIV video with in-person counseling in conveying disease-related knowledge and obtaining consent for HIV testing among adolescents seeking care at an urban emergency department (ED).

The two-armed, randomized controlled trial was conducted on a convenience sample of 200 stable, sexually active 15- to 21-year-olds. Participants in both the in-person counseling group and the video intervention group completed preintervention and postintervention HIV knowledge measures. The primary outcome measure was HIV knowledge, while the secondary outcome was consent for HIV testing. Characteristics associated with voluntary HIV testing were identified.

No difference in preintervention HIV knowledge scores was found between the groups. Mean postintervention knowledge scores differed significantly between the video (78.5 percent correct) and the counselor (66.3 percent) (P<.01) groups. In all, 51 percent of the video-watching group vs. 22 percent in
the control group accepted HIV testing (P<.01). Watching the video (odds ratio: 3.6 [95 percent confident interval: 1.8-7.2]), being female (OR: 2.1 [95 percent CI: 1.0-4.2]), engaging in oral sex (OR: 2.8 [95 percent CI: 1.4-5.9]) and being age 18 or older (OR: 3.8 [95 percent CI: 1.8-7.8]) were all positively associated with testing.

“A youth-friendly HIV educational video improved adolescents’ HIV knowledge and increased their participation in HIV testing more than in-person counseling. Video-based HIV counseling can perform as well or better than in-person counseling for adolescents in the ED,” the authors concluded.

**Scientists find genetic basis for key parasite function in malaria**

**NIH researchers show parasites create feeding ion channels in blood cells**

Snug inside a human red blood cell, the malaria parasite hides from the immune system and fuels its growth by digesting hemoglobin, the cell’s main protein. The parasite, however, must obtain additional nutrients from the bloodstream via tiny pores in the cell membrane. Now, investigators from the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, have found the genes that malaria parasites use to create these feeding pores.

The research was led by Sanjay A. Desai, M.D., Ph.D., of NIAID’s Laboratory of Malaria and Vector Research. In 2000, Dr. Desai co-discovered the primary type of feeding pore on parasite-infected blood cells, an ion channel known as the plasmodial surface anion channel (PSAC). Ion channels are pore-forming proteins that allow the movement of calcium, sodium and other particles into or out of the cell. A report of the team’s new findings, which build on this original discovery, is now online in Cell.

"Despite recent progress in controlling malaria worldwide, the disease continues to kill more than 700,000 people, primarily young children, every year," said NIAID Director Anthony S. Fauci, M.D. "Dr. Desai and his colleagues have discovered the genetic basis of a fundamental aspect of malaria parasite biology, and in doing so, they have opened up potential new approaches to developing antimalarial drugs."

Scientists have known for decades that malaria-infected red blood cells have greater nutrient uptake than non-infected cells, presumably to support parasite survival and growth, noted Dr. Desai. But, he added, "It was debated whether the parasite co-opts existing human channels or uses its own proteins to remodel the red blood cell membrane."

To answer this question, the NIAID team screened nearly 50,000 chemicals for their ability to block nutrient uptake by cells infected with either of two genetically distinct lines of Plasmodium falciparum malaria parasites, HB3 and Dd2. Most chemicals were equally active against the two lines, but one, ISPA-28, stood out because it was 800 times more active against the nutrient channels of Dd2-infected red blood cells than against those of HB3-infected cells.

If the PSAC protein is made by the parasite, the scientists reasoned, the strikingly different effects of ISPA-28 on the two lines may reflect genetic differences. To explore this possibility, the investigators measured how well ISPA-28 inhibited PSAC activity in daughter parasites resulting from a genetic cross between the HB3 and Dd2 lines. They found that most daughter parasites made channels that were identical to those of one or the other parent, indicating that parasite genes play an important role. The inheritance pattern of ISPA-28 action on channels led the researchers to chromosome 3, where they found two parasite genes, clag3.1 and clag3.2, that appear to encode the PSAC protein.

This genetic evidence was bolstered when they showed that individual parasites express either the clag3.1 gene or the clag3.2 gene, but not both simultaneously. They found that switching between the two genes produced changes in PSAC behavior that could be predicted. Malaria parasites use gene switching as a way to protect essential proteins from attack by the immune system, Dr. Desai explained.

"We were surprised to discover a role for clag genes in PSAC activity," said Dr. Desai. This family of genes, which do not look like other ion channel genes, was previously thought to be involved in helping infected cells adhere to the inner lining of blood vessels. Clag genes are found in all species of malaria.
parasites, noted Dr. Desai, and this fact, along with the discovery that the parasites can choose between one of two channel genes to ensure nutrient uptake, strongly suggest that PSAC is required for parasite survival within red blood cells.

The discovery of parasite genes required for PSAC activity opens up several new research directions, said Dr. Desai. For example, development of antimalarial drugs that target these channels could be accelerated. The NIAID team has already found PSAC inhibitors that kill malaria parasites. Dr. Desai’s team also is exploring how the PSAC protein is transported from the parasite to the red blood cell membrane, as preventing this transport may be another way to kill malaria parasites.

**Study finds 2 gene classes linked to new prion formation**

Unlocking the mechanisms that cause neurodegenerative prion diseases may require a genetic key, suggest new findings reported by University of Illinois at Chicago distinguished professor of biological sciences Susan Liebman.

Prions can turn a normal protein into a misfolded form. One prion in mammals promotes progressive neurodegenerative disorders like “mad cow” disease that often prove fatal. But how this process happens remains an open question for scientists.

Prions have been found to exist in a wide range of organisms. Those in brewer’s yeast, which researchers like Liebman study, provide critical insight into how prions work.

Prion proteins in yeast aggregate, while non-prion proteins do not. Aggregation of new prions happens spontaneously—but, in the natural world, very slowly.

Anita Manogaran, a former UIC research assistant professor in biological sciences, working with Liebman, speed-up prion formation to identify genes important in the process. The researchers were also able to monitor different stages of prion appearance by tagging prion proteins with another protein that fluoresces green. Cells in the process of forming prions had fluorescent rings, which could give rise to cells with prions.

"We learned there are some genes important for the generation of prions," Liebman said.

Some 400 yeast genes were screened for the ability to prevent the new appearance of yeast prion proteins.

"Through a number of screens, we came down to a much smaller number (of genes) that inhibited prion appearance," Liebman said. These genes fell into two classes—one that could still make the rings, which is the hallmark of the beginning of prion aggregation. But the other class of genes had trouble forming rings, Liebman said.

Liebman and Manogaran also looked beyond new prion formation to see if these same genes had an effect on toxicity associated with a protein that causes Huntington’s disease—a fatal human neurodegenerative disorder.

"We found that genes that could make rings also were more toxic in the presence of the Huntington’s disease protein," Liebman said. "If no rings were made, they were less toxic."

The full implications of the findings are not yet understood, Liebman cautioned.

"The more we understand about these mechanisms and the genes that are involved, the more we’ll be able to understand the new appearance of prion disease—like Creutzfeldt-Jakob and ‘mad cow’—and Huntington’s disease. The more we understand what affects toxicity, the more we’ll understand why these are toxic."

The findings were reported in the May 19 issue of PLoS Genetics.

**Wider Distribution of Drugs Needed to Cut AIDS Deaths in China**

*Reuters*, (05.19.2011) Tan Ee Lyn

Mortality among people with HIV/AIDS dropped greatly as China rolled out its antiretroviral therapy (ART) program, a new study shows. The state program began in 2003 and targeted mainly rural patients infected in the 1990s through unsanitary blood-buying schemes.

To cut AIDS deaths further, however, China also will have to reach out to treat those infected sexually and through needle sharing, noted Dr. Fujie Zhang, of the National Center for AIDS/STD Control and Prevention in Beijing, and colleagues. “Increased attention must be given to these populations, to diagnose HIV infection earlier, and increase treatment coverage,” they wrote.

Among treatment-eligible patients studied, mortality dropped from 39.3 per 100 person-years in 2002 to 14.2 per 100 person-years in 2009, while treatment coverage grew from almost zero to 63.4 percent, the study found.
“Treatment coverage for blood-donor HIV patients is up to 80 percent, and their mortality is 6.7 percent,” Zhang said. “But for injecting drug users, treatment there is only 43 percent and mortality is much higher at 16 percent.”

“Before ART, the mortality rate was 40 percent,” Zhang said. “After ART, it was 14.2 percent. Those on HAART [highly active antiretroviral therapy] had mortality of 5.7 percent.”

Of China’s official estimate of 740,000 people with HIV, 323,252 had been diagnosed by the end of 2009. Among them, 82,540 received free treatment—mainly those infected through blood-buying operations.

“HAART reduces mortality and increases quality of life, and if HAART is implemented on a larger scale, it reduces transmission in the population,” said Zhang. “Treating one person perfectly is meaningless, but treating many will bring transmission down. So we must increase coverage and then treat early.”


Red Ribbon on Twin Peaks Hill Marks First CDC Report of Disease
San Francisco Chronicle, (05.23.2011) Rachel Gordon

On Sunday, about 100 volunteers installed a giant red AIDS awareness ribbon on the eastern slope of San Francisco’s Twin Peaks to mark the 30th anniversary of the epidemic. CDC’s first report of the condition that would become known as AIDS was published on June 5, 1981. The ribbon is a project of the San Francisco AIDS Foundation (SFAF); it will remain on display until June 19.

San Francisco has been profoundly affected by HIV/AIDS. Through this March, 34,716 residents have been diagnosed with HIV; 19,393 have died of AIDS-related causes; and more than 15,000 are living with the virus. Activists worry, however, that today’s younger San Franciscans have little knowledge of the epidemic’s early years, when the disease devastated the city and angry demonstrators demanded access to treatment and an end to discrimination.

“We’re finding a new generation of people at risk who didn’t experience losing their loved ones, losing their friends,” said James Loduca, an SFAF vice president. "AIDS has always been a preventable disease, and 30 years later, it’s still here. But we will see an end to the disease.”

The ribbon is made of 15,000 square feet of plastic tarp and is held in place by 400 stakes. It should be visible from the East Bay on a clear day.

“Like an aging movie star, it's going to look better from a distance,” said Patrick Carney, who helped with the project.

Obama, Medvedev Reaffirm Efforts To Eradicate Polio Ahead Of G8 Summit

President Barack Obama met with Russian President Dmitry Medvedev in Deauville, France, ahead of the G8 summit, ABC News’ "Political Punch" blog reports. "The two issued a number of joint statements and agreements on counterterrorism, civil aviation security, visa issues, the Bering Strait region, a joint report assessing 21st Century Missile Challenges, innovation, the rule of law, smart grid partnership, eradicating polio, and medical research," according to the blog (Tapper/Miller, 5/26). "Obama and Medvedev recognized the collaborative efforts already underway between the United States and Russia to eradicate polio globally, and pledged to continue that cooperative until the eradication objective is finally achieved," a press release from USAID states (5/26).

Meanwhile, the Globe and Mail reports that G8 nations’ "deep fiscal emergencies" have almost dashed Canadian Prime Minister Stephen Harper's hopes of getting leaders to follow up on maternal health aid pledges. The newspaper highlights recent reports showing "the G8 nations are falling far short of both their maternal-health and their larger African aid pledges – and that the European countries, traditionally the largest donors to such humanitarian initiatives, are faring the worst."

"Canadian officials said in briefings that they want to see the G8 leaders issue a statement that renews their commitments to their Muskoka pledges to the maternal-health fund," the newspaper writes. Dimitri Soudas, the prime minister's communications director, said Harper planned to raise "the importance of delivering on commitments and monitoring their progress" (Clark/Saunders, 5/26).

Ahead of the start of the summit, the U.N. News Centre notes that U.N. Secretary-General Ban Ki-moon "is due to participate in sessions of the so-called G8 Outreach Programme, where he is expected to..."
continue to advocate for sustained attention to women’s and children’s health as a cornerstone of the global development agenda” (5/26).

Also on Thursday, a "drag queen in a sequin dress and pink boa made a surprise appearance at the G8 summit" to criticize "leaders’ unkept promises to provide AIDS treatment around the world," Agence France-Presse reports. "A small group of protesters handed out flyers announcing 'Miss Promise – guest of honour at the G8' and 'Unkept promises are promises that kill' inside the tightly secured press room in the France’s northern resort of Deauville," the news service writes (5/26).

**Intestinal cell defense mechanism against bacteria**

**Molecular mechanism of selected autophagy elucidated**

FRANKFURT. Salmonella is widely prevalent in the animal kingdom. The reason we do not suffer from severe intestinal infections very often is due to our body’s defence system, which manages to digest invading bacteria. This is why, generally speaking, a healthy human being will only fall ill if he consumes more than 100,000 salmonella bacteria via a contaminated food source, such as eggs or meat. An international team of researchers, led by Prof. Ivan Dikic from the Goethe University in Frankfurt has now found out how body cells recognise salmonella and render it harmless. Understanding this process at a molecular level is crucial in identifying new targets for treatment. Tropical and sub-tropical countries in particular, where various sub-species of salmonella are common, are experiencing a rapid increase in resistance to antibiotics, with children at greatest risk.

Salmonella infection begins with bacteria entering the epithelial cells of the intestinal mucosa. To prevent them multiplying there, special cell organelles, called autophagosomes are activated. These encircle the invaders and then become absorbed in other organelles – lysosomes – that contain certain special digestive enzymes, which break down the bacteria into their constituent parts. But how exactly do the autophagosomes recognise salmonella? Prof. Ivan Dikic and his research group at the Biochemistry Institute II have now shed light on this mechanism.

As reported in a current article in the scientific journal "Science", the salmonella are marked as ‘waste material’ by the molecule ubiquitin. In order for the autophagosomes to become active, the marked bacteria have to bind to another molecule – LC3 – on the autophagosomal membrane. Here, the protein optineurin plays a key role, linking the marked Salmonella to the autophagosomal LC3, thereby setting off a process of selective autophagy. But optineurin becomes active as a link only after being chemically modified by an enzyme, (in this case it is phosphorylated by the protein kinase TBK1). "We suspect that phosphorylation acts as a regulated switch to trigger selective autophagy of bacteria but might also prove significant in other cargoes like protein aggregates or damaged mitochondria" explains Prof. Ivan Dikic, underlining the importance of these findings. It is thought that impaired autophagy processes may be implicated in, among other things, the development of cancer as well as neurodegenerative diseases.

In the area of infectious diseases, these findings are particularly relevant in view of the fact that gastrointestinal disease caused by Salmonella enterica has rapidly increased since the mid-1980s. In Germany, approx. 30,000 cases were reported to the health authorities in 1985, but by 2005 the figure has risen to 52,000. Worldwide, 94 million people fall ill each year with acute gastroenteritis, and 155,000 of these die. Typhoid, a disease also caused by Salmonella, affects 16 million people annually and mortality rates reach 200,000, with children in particular falling victim to the disease. Bacteria are becoming increasingly resistant to antibiotics so that the potential for treating disease is limited. Chloramphenicol, a formerly popular broad-spectrum antibiotic, is now ineffective, and even Fluoroquinolones, currently a commonly prescribed antibiotic, is proving inadequate in fighting bacteria. As co-author Prof. Dirk Bumann from the Biozentrum at Basel University puts it: "There is a pressing need to find new forms of treatment for infectious diseases. A better understanding of how the body's own defence mechanism makes use of autophagy will certainly help."

**Publication:** Philipp Wild et al: Phosphorylation of the Autophagy Receptor Optineurin restricts Salmonella growth, *Science* 26th May 2011 advanced online publication (*Science* DOI: 10.1126/science.1205405)
Innate Immune System Proteins Attack Bacteria by Triggering Bacterial Suicide Mechanisms

ScienceDaily (May 27, 2011) — A group of proteins that act as the body's built-in line of defense against invading bacteria use a molecular trick to induce bacteria to destroy themselves, researchers at the Indiana University School of Medicine have determined. The research could point the way toward new anti-bacterial treatments that could take on bacteria that are resistant to antibiotics.

The proteins, called Peptidoglycan Recognition Proteins (PGRPs), are able to detect and target bacteria because bacteria are unique in having peptidoglycan polymers in their cellular walls. However, the mechanism by which PGRPs are able to kill bacteria had not been determined.

A research team led by Roman Dziarski, Ph.D., professor of microbiology and immunology at Indiana University School of Medicine—Northwest, reported May 22 in the advance online edition of the journal *Nature Medicine* that the PGRPs are able to induce a suicide response in the targeted bacteria.

The PGRPs accomplish the mission by binding to specific sites in bacterial cell walls in ways that exploit a bacterial defense mechanism known as protein-sensing two-component systems. These systems, which normally enable the bacteria to detect and eject malformed proteins, interpret the PGRPs as just such malformed proteins. Unable to dislodge the PGRPs, the bacteria then activate a suicide response, the researchers said.

This approach is different than those employed by other anti-bacterial mechanisms, such as the immune system’s white blood cells, said Dziarski.

"This could be a target to develop new anti-bacterial applications," Dziarski said.

Dziarski and colleague Dipika Gupta, Ph.D., associate professor of biochemistry and molecular biology at Indiana University School of Medicine—Northwest, first cloned the PGRP genes in 2001. The PGRP genes, which are found in species ranging from insects to mammals, are part of the body's innate immune system, in contrast to the mechanisms that learn and develop new immune responses to infections over time.

The PGRP proteins are normally expressed in phagocytic cells in blood and on body surface areas such as skin, mouth, intestine and other tissues that have direct or indirect contact with the external world, Dziarski noted. In some tissues it appears that the PGRPs help maintain a healthy relationship between the body and certain beneficial bacteria. Some studies have indicated that the loss of the PGRP proteins may lead to inflammatory bowel disease, suggesting that the research reported on May 22 could point the way to new approaches to target such problems, Dziarski said.

**Journal Reference:**
Des Raj Kashyap, Minhui Wang, Li-Hui Liu, Geert-Jan Boons, Dipika Gupta, Roman Dziarski. *Peptidoglycan recognition proteins kill bacteria by activating protein-sensing two-component systems.* Nature Medicine, 2011; DOI: [10.1038/nm.2357](http://dx.doi.org/10.1038/nm.2357)
**Improving DNA Sequencing: Sponge-Like Biosensor Crams Enormous Power Into Tiny Space**

ScienceDaily (May 27, 2011) — Vanderbilt University engineers have created a "spongy" silicon biosensor that shows promise not only for medical diagnostics, but also for the detection of dangerous toxins and other tiny molecules in the environment. This innovation was originally designed to detect the presence of particular DNA sequences, which can be extremely helpful in identifying whether or not a person is predisposed to heart disease or certain kinds of cancer. The new sensor is described in the Optical Society's open access journal, *Optics Express*.

Biological chemical sensors save lives by detecting dangerous substances in the environment or specific molecules in the blood that could signal life-threatening diseases. Current sensor technologies, however, are limited because of their large size compared to the extremely minute sizes of some of the chemicals to be detected. In most cases, when attempting to sense something very small with a large sensor, the small molecules don't perturb the sensor's properties enough for detection.

As Vanderbilt University’s Xing Wei, a graduate student, and Sharon M. Weiss, an associate professor of electrical engineering and physics, report in *Optics Express*, it’s possible to eliminate this challenge by making sensors with features that are comparative in size to the molecules being detected, greatly increasing the sensitivity of current sensing technology.

To do this, the engineers turned to a porous silicon material, which acts essentially as a small sponge that can then be "seeded" or filled with all sorts of substances that change its properties—resulting in a detector that’s highly sensitive to small molecules. Capturing a particular sequence of DNA involves seeding the sensor with a single strand of DNA, so that only the complementary strand can attach to it and everything else gets rinsed away.

Why use a porous silicon material? Weiss and Wei stress the significance of their new sensor’s enormous surface area relative to its small size. To illustrate this point, Weiss describes two cubes, one of which is 3 cm on a side, with a flat surface that DNA can be attached to—providing 54 cm² of available surface area to attach these molecules. The other is an identical-size cube, made into a porous silicon sponge and with the ability to access the volume of the cube with all of the internal surface area, providing a surface area that is nearly 10,000 times greater than the first cube. This is like comparing the area of a golf ball to the area of a football field—with the same footprint. "It's an enormous increase in the potential of how many molecules you can capture, and this is one reason why our new sensor is so much more sensitive for detecting small molecules," says Weiss.

And by using a "grating," a type of surface texturing of the porous silicon commonly used in sensors of this type, light can be delivered in a very simple and compact way to probe the change in the sensor's properties to determine whether or not any molecules of interest have been captured.

"If you look at a CD or a DVD in the light, you'll notice lots of colors bounce off it in room light. The way these discs work is that there are a bunch of bumps, which are very similar to our gratings," says Weiss. When light interacts with a particular arrangement of bumps, the engineers can essentially tell the light what to do, enabling readout of the music or videos on the disc.

That's precisely what the Vanderbilt team has done with their sensor—put bumps on top of it to control how the light interacts with their active sensing medium (the porous silicon "waveguide"). Then
they can determine what the signal means based either on the color that comes out or by the angle of light as it exits the sensor.

"When we infiltrate the molecules that we want to detect and they stay in the sensor and attach, they change the optical density of the porous silicon and, consequently, the angle or the color of light that comes back out," Weiss elaborates. "By knowing how much the angle changes, for example, we can quantify how many molecules are present. So not only can we identify our DNA sequence or toxin, but we can also know how much is present as well. For diagnostics, it's very helpful to know how much is present."

Other potential applications beyond DNA sensing may include detecting small molecules—such as toxins in the environment—which has significant national security implications.

**Journal Reference:**
Xing Wei and Sharon M. Weiss. *Guided mode biosensor based on grating coupled porous silicon waveguide.* Optics Express, Volume 19, Issue 12, pp. 11330-11339 [link]

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**DNA-RNA mismatch**

There may be widespread, nonrandom differences between DNA sequences and their corresponding RNA transcripts in human cells

[Published 19th May 2011 06:00 PM GMT]

The central dogma in molecular biology states that DNA is copied into RNA, one nucleotide at a time. But it turns out that copy may be a lot less exact than scientists previously thought.

A new paper, published today in *Science,* identifies widespread differences between DNA sequences and their corresponding RNA transcripts in human cells, and demonstrates that these differences result in proteins that do not precisely match the genes that encode them.

The finding challenges the assumption that RNA is a perfect one-to-one match to its corresponding DNA sequence and may open the door to an unexplored area of variation in the human genome.

"Most people assume the information in DNA is faithfully transferred to RNA and then the RNA is translated into proteins," said Jin Billy Li, a geneticist at Stanford University who was not involved in the research. If additional research confirms the results, "the central dogma will have to be revised. You can't assume the DNA [code] is transferred to RNA without any changes."

Vivian Cheung and colleagues at the University of Pennsylvania School of Medicine used next generation sequencing tools to sequence RNA from B cells of 27 individuals who were part of the International HapMap and 1000 Genomes Projects. They then compared those RNA sequences to their corresponding genes in the DNA.

Cheung was surprised to find more than 10,000 sites where RNA bases did not match the corresponding DNA sequence. "We didn't really expect anything, and then we saw a lot of differences," says Cheung. Her initial reaction was to blame the differences on technical errors or artifacts, so the team performed numerous experiments to rule out a technical fluke.

In the process, they noticed that many of the differences were not random. Time and again, a single RNA base was always changed in the exact same way from cell to cell. A site that should be AA might be edited to AC, for example, and every individual would either have the original AA or the edited AC, but no other possible modifications, such as AG or AT.

Then the team looked at the resulting proteins and found that they reflected the edited RNA sequences, meaning the DNA did not directly encode its protein products. In some cases, the changes were minor, but not all. In one, a RNA variant led to the loss of a stop codon, and the protein was 55 amino acids longer than would have been encoded by the DNA.

Past research has identified several post-transcriptional mechanisms that result in RNA editing, but these mechanisms account for less than half of the differences uncovered in the new study, the authors write. Cheung and the team do not yet know the mechanisms that might be causing the systematic RNA modifications, nor how the resulting protein changes might affect protein function.

Still, "this is one source of genomic variation we didn't know about," says Cheung. "We always think of DNA sequences as the causes or reasons why some of us are more or less prone to certain diseases, but we certainly didn't think RNA sequences as being the possible cause. And now we have all these forms of proteins we didn't know existed."

But additional research needs to be done to confirm the findings, said Li, who is performing similar studies in his lab. "Mapping these differences is not a trivial thing," he cautioned. Many genes exist two or
more times in the human genome, and researchers could mistakenly map an RNA sequence to the wrong region. "If that happens, you may miscall that as RNA editing," he said.


Dogma
by anonymous poster, [Comment posted 2011-05-26 14:11:50]

Dogma states that information flows from DNA to RNA to protein. It does not exclude that this flow can be context dependent, or even subject to feedback. Transcriptional, post-Transcriptional, Translational, and post-Translational modifications to not change the fact that the core information is in the DNA. Even the information to create the modification systems are typically of genomic origin. It will be interesting to learn the mechanism behind the differences found in these new experiments, and where it is employed besides lymphocytes.

Baxter Zappa
This is likely both a true finding and a general phenomenon
by DENNIS HOLLENBERG, [Comment posted 2011-05-24 11:06:56]

We do not know the exact set of mechanisms causing this, or any other transcription-phase modification (or post-transcription mods, for that matter). I say the mechanism likely involves operations performed by trans or _preexisting_ ribosomal-protein complexes. Regardless, Cheung and colleagues performed masterfully.

The central dogma states that cellular genetic information flows exclusively from DNA to RNA to proteins. Cheung et al. show that RNA modification information can come from some place else.

Keep in mind that DNA isn’t “smart.” DNA is but a substrate of molecular information harvested and transformed by the cell’s molecular networks in often custom ways suited to the local part of the cell’s microenvironment.

The problem with the glib central dogma is that it answers a question that is wrong headed. That is, the central dogma assumes that the cell is a centrally controlled machine. It is not. In fact, modifications occur generally, universally. Therefore, the central dogma is irrelevant and has always been so. Get real, folks.

Generalized phenomenon, or specific to the immune system?
by anonymous poster, [Comment posted 2011-05-20 12:02:14]

My biggest question is as to how widespread this effect will be. B cells in particular undergo a number of unique DNA rearrangements that are not seen in other cells, presumably to increase the number of unique antibodies that our immune system can produce. What if extensive RNA editing is merely another strategy to increase heterogeneity? Most cells do not require, and likely actively avoid, such levels of variation, making it possible that this is not a generalized phenomenon outside of the immune system.

Epimutations and Dogma
by anonymous poster, [Comment posted 2011-05-20 05:46:24]

It has been known for a while that there are other forms of epimutations besides aberrant DNA methylation changes, such as posttranscriptional mutations. The news is therefore not surprising in itself. The interesting aspect is the scale.

The findings do not invalidate the central dogma in any way and saying so rests on erroneous assumptions. The dogma was always a stipulation about the direction of the information flow, and a negative one at that (saying that the information in the protein sequence could not be used for de novo synthesis of DNA, RNA or Proteins with equivalent information content). The existence of large scale posttranscriptional mutations/variation does not invalidate this directional flow. Prions are therefore not challenging the letter of the central dogma as such (configurational rather than sequential self-replication), but rather its spirit.

By Megan Scudellari

An autism brain signature?
A set of molecular pathways abnormally expressed in the brains of autism patients may provide new therapeutic targets
[Published 25th May 2011 06:00 PM GMT]

A genome-wide analysis of the RNA in the brains of individuals with autism reveals consistent patterns of abnormal gene expression and implicates several molecular pathways in the pathology of autism.

The research, published today in Nature, suggests that shared molecular pathways underlie autism, a notoriously heterogeneous disease, which may point the way to biomarkers and therapeutic targets for the disease.

"Here, using an unbiased genome-wide scanning method looking at the RNA rather than the DNA, we clearly identify these two major processes going on that are common to a majority of autism brains," said senior author Daniel Geschwind of the University of California, Los Angeles.

"This is really well done study, with appropriate sample sizes and well thought through," said Karoly Mirnics, a neuroscientist at Vanderbilt University who was not involved in the research. "We need more of these kinds of rigorous studies."

Instead of comparing DNA sequences of people with autism against normal controls, as done in many genome-wide association studies, Geschwind and colleagues decided to look at the mRNA, or transcriptome, of individuals with autism to identify any abnormalities in gene expression.

They compared brain tissue samples from 19 autism patients with 17 controls and measured the abundance of mRNA in the cerebellum and cerebral cortex. In total, 444 genes were differentially expression in the autism cortex samples. And there was a surprising pattern: In normal brains, gene expression in frontal lobe varies significantly from that in the temporal lobe due to the different functions
of the two regions of the brain. But in autism brains, the levels of gene expression between the two lobes were homogenized, as if the two regions did not have disparate functions.

"The paper implies that the different brain regions in autism are not specialized as they should be," said Mirnics, who wrote an accompanying News & Views article in Nature. "It very well might be the result of impaired development." This pattern of abnormal gene expression was shared by more than two-thirds of the autism patients, suggesting that the altered molecular pathways are common in brains with autism, an important and debated point in autism research. Because autism cases vary widely in terms of phenotype and only a few genes have been implicated across the whole spectrum of autism disorders, researchers have suspected that there are no common causes of the disease, making it extremely hard to develop widely applicable autism therapies.

"If you have 100 cases of autism, we used to think there were 110 mutations," said Geschwind. "This is now telling us there are common patterns."

To further explore the differences, the team focused on two networks where altered gene expression of one or a few genes appeared to be driving the abnormal expression of a group of interacting genes. One of these was A2BP1, a master gene splicer. The team found that A2BP1 was downregulated in brains with autism, and resulted in the abnormal splicing of genes involved in synaptic function. A second network included multiple astrocyte markers, ADFP and IFITM2, whose upregulated expression affected immune and inflammatory genes.

Using a technique called network analysis to organize the data, the team compared their findings to genome-wide association studies of non-psychiatric disease, and concluded that the A2BP1 network of affected genes is genetically associated with autism and could even be causal, while the over expression of immune genes was not. Together, the two processes show a high degree of correlation, but "the immune response is probably secondary" to synaptic dysfunction or caused by environmental factors, said Geschwind.

It will take time to understand how these molecular pathways are connected, but the identification of common, abnormally expressed molecular pathways in this heterogeneous disease provides hope that common treatments can be developed for individuals all along the autism spectrum. "It provides a springboard for focused studies that should get us more quickly to therapies," said Geschwind.


Can Cannabis Reduce HIV Disease Progression?

**SUMMARY**

THC, the main psychoactive component in marijuana, was associated with decreased viral load and lower risk of death in monkeys infected with a virus related to HIV.

By Liz Highleyman

Cannabis has been shown in studies to improve appetite, relieve chronic pain, and reduce nausea due to chemotherapy. Many people with HIV/AIDS use medical marijuana to combat wasting and other symptoms, which raises questions about what effects it might have on HIV and its progression.

Many immune cells express cannabinoid receptors, indicating that cannabis may influence immune function. Some prior research suggested that marijuana use is associated with HIV disease progression, but such studies were prone to confounding by socioeconomic and other factors related to illegal drug use.

As described in the June 2011, issue of AIDS Research and Human Retroviruses, Patricia Molina and colleagues from Louisiana State University Health Sciences Center examined the impact of ongoing administration of delta-9-tetrahydrocannabinol (THC) in macaque monkeys exposed to simian immunodeficiency virus (SIV).

Eight rhesus macaques received twice-daily intramuscular injections of either THC or a placebo. After 28 days, they were intravenously inoculated with a highly infectious dose of SIV. The researchers looked and immune and metabolic indicators of disease progression during the initial 6-month asymptomatic phase after infection.

**Results**

- THC administration did not significantly increase viral load or exacerbate immune dysfunction.
- After exposure to SIV, the monkeys showed measurable viral loads, decreased CD4/CD8 T-cell ratios, and increased CD8 cell proliferation.
Administration of cannabis prior to infection produced little or no effects on these parameters.

THC-treated monkeys lost CD4 cells more slowly than the placebo group.

Monkeys given THC had a significantly lower early mortality rate compared with placebo-treated animals.

THC-treated monkeys had lower plasma and cerebrospinal fluid SIV viral load than those in the placebo group.

Monkeys in the THC group also experienced less wasting, though the difference did not reach statistical significance.

In a laboratory study, THC decreased SIV replication in MT4-R5 cells in vitro.

"These results indicate that chronic [THC] does not increase viral load or aggravate morbidity and may actually ameliorate SIV disease progression," the study authors concluded.

"Two of the [placebo-treated] animals succumbed to SIV infection shortly after 5 months, and a third reached end stage at 7 months," they elaborated in their discussion. "Among the [THC-treated] animals, the first animal did not reach end stage until 11 months post-SIV inoculation."

"We speculate that reduced levels of SIV, retention of body mass, and attenuation of inflammation are likely mechanisms for [THC]-mediated modulation of disease progression that warrant further study," they wrote. 5/31/11

Reference

TBR-652 Inhibits HIV, May Dampen Inflammation

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<th>SUMMARY</th>
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<td>TBR-652, a drug that blocks both CCR5 and CCR2 cell receptors, showed potent antiviral activity against HIV, but did not change most inflammation biomarkers.</td>
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By Liz Highleyman

HIV uses 2 different surface co-receptors—CCR5 and CXCR4—along with the CD4 receptor to enter T-cells. CCR5 antagonists such as maraviroc (Selzentry) prevent HIV from entering cells by blocking this co-receptor.

Tobira’s investigational drug TBR-652 blocks both CCR5 and CCR2, a receptor that binds to monocyte chemoattractant protein 1 (MCP-1, also known as CCL2), a chemical messenger that promotes migration of monocytes and macrophages.

Though not fully understood, CCR2 plays a role in inflammation and has been studied in inflammatory conditions such as atherosclerosis and metabolic syndrome. A growing body of evidence indicates that ongoing immune activation and persistent inflammation may contribute to a range of non-AIDS conditions in people with HIV.

In 2010, researchers presented data from a proof-of-concept study of TBR-652 in HIV positive people at CROI and at the International AIDS Conference in Vienna. Their findings have now been published in the June 1, 2011, Journal of Acquired Immune Deficiency Syndromes.

This double-blind Phase 2 study included 52 participants in the U.S. and 2 in Argentina with confirmed CCR5-tropic (using the CCR5 co-receptor) HIV. Most were men, the average age was about 40 years, and the mean CD4 T-cell count was about 450 cells/mm3. They were treatment-experienced but had never used CCR5 antagonists and had been off all ART for at least 6 weeks at study entry.

Participants were randomly assigned to receive TBR-652 monotherapy at oral doses of 25, 50, 75, 100, or 150 mg per day, or else placebo, once-daily for 10 days. The 100 mg dose group used a different formulation that was later discontinued; these patients—which included the 2 in Argentina—were excluded from the efficacy analysis but included in the safety analysis.

At days 1 and 10 the researchers measured HIV RNA and biomarkers associated with inflammation, including MCP-1, high-sensitivity C-reactive protein (hs-CRP), and interleukin 6 (IL-6). Elevated MCP-1 was used as an indicator of effective CCR2 blocking.

Results

TBR-652 demonstrated potent anti-HIV activity, significantly greater than that of placebo.
Maximum median decreases in HIV RNA from baseline were -0.7, -1.6, -1.8, and -1.7 in the 25, 50, 75, and 150 mg dose groups, respectively, compared with -0.3 in the placebo group.

33%, 71%, 100%, and 75% of patients in respective TBR-652 dose groups achieved viral load reductions of at least 1 log.

Participants reached a nadir or lowest HIV viral load after a median of 10-11 days, or just after the last dose.

At 10 days levels of MCP-1 increased significantly in the 50 mg and 150 mg dose groups, by about 100 and 300 pg/mL, respectively.

The average CRP level decreased, but this was mainly attributable to a single participant with a high baseline level due to acute inflammation.

Effects on other immune or inflammation markers including hs-CRP and IL-6 levels were "negligible."

CD4 cell count also did not change significantly during the short dosing period.

TBR-652 was generally safe and well-tolerated at all doses studied.

No severe adverse events or laboratory abnormalities were observed in any TBR-652 dose group, and no participants withdrew due to side effects.

Based on these results, the study authors concluded, "TBR-652 caused significant reductions in HIV-1 RNA at all doses. Significant increases in MCP-1 levels suggested strong CCR2 blockade."

"TBR-652 was generally well tolerated with no dose-limiting adverse events," they continued. "[Pharmacodynamic characteristics] indicate that TBR-652 warrants further investigation as an unboosted, once-daily, oral CCR5 antagonist with potentially important CCR2-mediated anti-inflammatory effects."

In their discussion they noted that since the lowest viral loads were observed on average on days 10-11, as treatment was ending, "a true nadir may not have been reached in the 10-day treatment," suggesting viral levels might decline further with longer therapy.

Tobira is now conducted a Phase 2b clinical trial with various substudies to evaluate immunological, cardiovascular, and metabolic parameters, "with the hopes of clarifying their usefulness in predicting inflammatory processes and reducing the risk of inflammatory disease with TBR-652 therapy." Drug interaction studies are also underway to enable construction of a combination regimen with an appropriate TBR-652 dose. 5/31/11

Reference

New Delhi metallo-beta-lactamase-1 enzyme acquired in Canada
An enzyme associated with extensive antibiotic resistance called New Delhi metallo-β-lactamase-1 (NDM-1), endemic in India and Pakistan and spreading worldwide, has been found in two people in the Toronto area, one of whom acquired it in Canada, states a case report in CMAJ (Canadian Medical Association Journal) (pre-embargo link only) http://www.cma.j.ca/embargo/cmaj110477.pdf. The report outlines challenges and approaches to managing and identifying this pathogen, which is highly resistant to treatment.

NDM-1 has spread because of worldwide travel, medical tourism and its ability to transfer between bacteria.

In one of the cases in this report, the patient had not travelled outside southwestern Ontario in over a decade, and no source could be identified for the organism. In the other case, the patient had been hospitalized in India for a medical procedure and acquired the organism there.

"These two scenarios show that local acquisition of an organism producing NDM-1 has already occurred in Ontario, Canada, that blaNDM-1 has been found in bacterial species other than [Escherichia coli] and [Klebsiella pneumoniae], that treatment options are limited for infections with NDM-1-producing organisms, and that the detection of NDM-1-producing organisms by a laboratory can be difficult," writes Dr. Susan Poutanen, Mount Sinai Hospital and University Health Network, with coauthors.
In the case of the patient who had not travelled, the authors note: "To the best of our knowledge, this is the first reported instance in which an NDM-1-producing organism was locally acquired in Canada."

In cases where patients are infected with NDM-1, extensive infection control precautions must be taken, including isolation in single rooms and enhanced cleaning.

"European guidelines recommend even more precautionary approaches to protecting patients admitted to hospital and suggest that all hospitals should have preparedness plans in place," state the authors.

Laboratory detection of the pathogen is also difficult, and labs should adopt different screening procedures.

**New malaria protein structure upends theory of how cells grow and move**

Researchers from the Walter and Eliza Hall Institute have overturned conventional wisdom on how cell movement across all species is controlled, solving the structure of a protein that cuts power to the cell 'motor'. The protein could be a potential drug target for future malaria and anti-cancer treatments.

By studying the structure of actin-depolymerising factor 1 (ADF1), a key protein involved in controlling the movement of malaria parasites, the researchers have demonstrated that scientists' decades-long understanding of the relationship between protein structure and cell movement is flawed.

Dr Jake Baum and Mr Wilson Wong from the institute's Infection and Immunity division and Dr Jacqui Gulbis from the Structural Biology division, in collaboration with Dr Dave Kovar from the University of Chicago, US, led the research, which appears in today's edition of the *Proceedings of the National Academy of Sciences* USA.

Dr Baum said actin-depolymerising factors (ADFs) and their genetic regulators have long been known to be involved in controlling cell movement, including the movement of malaria parasites and movement of cancer cells through the body. Anti-cancer treatments that exploit this knowledge are under development.

"ADFs help the cell to recycle actin, a protein which controls critical functions such as cell motility, muscle contraction, and cell division and signaling," Dr Baum said. "Actin has unusual properties, being able to spontaneously form polymers which are used by cells to engage internal molecular motors – much like a clutch does in the engine of your car. A suite of accessory proteins control how the clutch is engaged, including those that dismantle or 'cut' these polymers, such as ADF1.

suggested that the ability of ADFs to dismantle actin polymers – effectively disengaging the clutch – required a small molecular 'finger' to break the actin in two," Dr Baum said. "However, when we looked at the malaria ADF1 protein, we were surprised to discover that it lacked this molecular 'finger', yet remarkably was still able to cut the polymers. We discovered that a previously overlooked part of the protein, effectively the 'knuckle' of the finger-like protrusion, was responsible for dismantling the actin; we then discovered this 'hidden' domain was present across all ADFs."

Mr Wong said that the Australian Synchrotron was critical in providing the extraordinary detail that helped the team pinpoint the protein 'knuckle'. "This is the first time a 3D image of the ADF protein has been captured in such detail from any cell type," Mr Wong said. "Imaging the protein structure at such high resolution was critical in proving beyond question the segment of the protein responsible for cutting actin polymers. Obtaining that image would have been impossible without the synchrotron facilities."
Dr Baum said the new knowledge will give researchers a much clearer understanding of one of the fundamental steps governing how cells across all species grow, divide and, importantly, move. "Knowing that this one small segment of the protein is singularly responsible for ADF1 function means that we need to focus on an entirely new target not only for developing anti-malarial treatments, but also other diseases where potential treatments target actin, such as anti-cancer therapeutics," Dr Baum said. "Malaria researchers are normally used to following insights from other biological systems; this is a case of the exception proving the rule: where the malaria parasite, being so unusual, reveals how all other ADFs across nature work."

More than 250 million people contract malaria each year, and almost one million people, mostly children, die from the disease. The malaria parasite has developed resistance to most of the therapeutic agents available for treating the disease, so identifying novel ways of targeting the parasite is crucial.

Dr Baum said that the discovery could lead to development of drugs entirely geared toward preventing malaria infection, without adverse effects on human cells. "One of the primary goals of the global fight against malaria is to develop novel drugs that prevent infection and transmission in all hosts, to break the malaria cycle," Dr Baum said. "There is a very real possibility that, in the future, drugs could be developed that 'jam' this molecular 'clutch', meaning the malaria parasite cannot move and continue to infect cells in any of its conventional hosts, which would be a huge breakthrough for the field."

**FDA Updates Enfuvirtide (Fuzeon) Label with New Data on Incidence of Bacterial Pneumonia**

“Updates to the Warnings and Precautions, Pneumonia subsection of the Fuzeon (enfuvirtide) package insert were approved on April 28, 2011 in response to results of a study conducted under a Postmarketing Commitment. Drug sponsor, Roche, submitted the results from an ‘Observational Cohort Study on the Incidence of Pneumonia in HIV-1 Patients Treated with Fuzeon.’ …

“The findings from the study are included in Warnings and Precautions section 5.3 Pneumonia of the package insert as follows. …

“Because it was unclear whether the higher incidence rate of pneumonia was related to FUZEON use, an observational study in 1850 HIV-infected patients (740 FUZEON treated patients and 1110 non-FUZEON treated patients) was conducted to evaluate the risk of pneumonia in patients treated with FUZEON. A total of 123 patients had a confirmed or probable pneumonia event in this study (62 in the FUZEON treatment arm with 1962 patient-years of observation and 61 in the non-FUZEON treatment arm with 3378 patient-years of observation). The incidence of pneumonia was 3.2 events/100 patient-years in the FUZEON treatment arm and 1.8 events/100 patient-years in the non-FUZEON treatment arm. The hazard ratio, adjusting for other baseline risk factors, was 1.34 (95% C.I. = 0.90 – 2.00). Based on this observational study, it is not possible to exclude an increased risk of pneumonia in patients treated with FUZEON compared to non-FUZEON treated patients.”

By Gayatri Vedantam and Glenn S. Tillotson

**Wrestling with Recurrent Infections**

*Clostridium difficile* is evolving more robust toxicity, repeatedly attacking its victims, and driving the search for alternative therapies to fight the infection.

As infectious bacteria go, *Clostridium difficile* may be one of the most vexing for researchers, clinicians, and patients alike. It spreads from person to person by ingestion of the bacterium’s spores, which can not only remain viable for long periods of time outside of a human host, but can withstand most common disinfectants. Within the body, the spores can survive the acidity of the stomach, germinating in the intestines where the bacteria release toxins that wreak havoc on the bowel, causing severe abdominal pain and diarrhea. And while the proper regime of antibiotics usually eliminates the infection, residual spores can remain, and the bacteria can reemerge with a vengeance weeks or months later.
Recent estimates suggest that *C. difficile* infections (CDI) are on the rise, with up to 3 million cases in the United States each year, and a third or more of CDI patients experience recurrence of the disease within the first month. Furthermore, recently evolved hypervirulent strains of *C. difficile* produce robust amounts of the disease-causing toxins, more spores, and additional surface proteins that help *C. difficile* persist in the gut and environment. Clearly, novel therapies are needed to combat the bacterium.

The case of Gertrude Smith (whose name was changed to protect her identity) a generally healthy 82-year-old grandmother living in Rhode Island, illustrates just how difficult treating CDI can be. She went to her doctor complaining of a bad cough, low fever, and chest pain. Her doctor prescribed a 10-day course of antibiotics, a decongestant, and bed rest for a presumed chest infection. But within a week, Smith had developed profuse, watery diarrhea, and she returned to her doctor for help.

She was eventually admitted to the ER, diagnosed with a *C. difficile* bacterial infection, and prescribed the recommended antibiotic treatment—500 milligrams of metronidazole three times a day for 10 days. Two weeks later, however, when she started a different antibiotic to address a persistent cough and chest pain, the diarrhea returned. Another cycle of metronidazole seemed to do the trick, until six months later, when her doctor prescribed yet another antibiotic for urinary symptoms, and she was once again hit with intolerable diarrhea. This time it was even more violent than before, and accompanied by acute abdominal pain. A double dose of traditional antibiotics temporarily quelled her symptoms, but four months later, the cycle started all over again. *C. difficile* was repeatedly attacking this otherwise healthy woman, with increasing intensity each time it struck.

Unfortunately, with rising rates of CDI in the United States and around the world, Smith’s experience is not that uncommon. Last year, CDI surpassed methicillin-resistant *Staphylococcus aureus* (MRSA) as the leading cause of hospital-acquired bacterial infection in the United States, and now also occurs in community settings with greater regularity, possibly transmitted through newly recognized sources such as raw and cooked food. To make matters worse, as many as 40 percent of CDI patients experience a recurrence of the infection, and patients who have already experienced more than one CDI episode have an estimated 50–65 percent chance of having another acute attack. And while CDIs were once rarely reported in children, two reports in 2010 revealed that CDI rates among hospitalized children in the United States have doubled over the past decade.

Not only are *C. difficile* infections becoming more widespread, the symptoms appear to be getting more severe. Recent startling data from the United Kingdom showed that nearly 30 percent of patients over the age of 60 and more than 41 percent of patients over 90 died within 30 days of infection—significantly higher than previously estimated. In the United States, mortality rates from CDI more than quadrupled from 1999 to 2004. So just as MRSA was the bug of the 1990s, it is becoming clear that *C. difficile* can justly be considered the bug of the new millennium.

Recent work shows that the increase in CDIs has been accompanied by the appearance of particularly virulent strains of the pathogen. And although antibiotic resistance is not yet a major therapeutic issue with *C. difficile*, some strains have started to...
show resistance to quinolones (Cipro and Levaquin) and some macrolide antibiotics (Biaxin), likely contributing to the selective pressures driving the evolution of the organism.

Fortunately, novel therapies are being developed to combat even the most pathogenic strains of C. difficile. New antibiotics, for example, have already shown encouraging potential in defeating this dreaded microbe and reducing high levels of recurrence, while complementary approaches focus on preventively fighting back even before patients are infected. Though still in early stages, preliminary results are promising, and some experts believe that a combination of antimicrobial, immunological, and biotherapeutic techniques may provide a breakthrough in the battle against CDI. Used appropriately—at the right times, and in the right patient populations—these new therapies should help reduce not only the incidence of the disease and the incessant recurrences seen with current therapies, but also alleviate the impact of CDI on human lives and economies.

One bad bacterium
CDIs are usually contracted by ingestion of *C. difficile* bacteria and their spores. While most of the bacteria die upon contact with the stomach’s acidic environment, the spores survive, passing on to the intestines where they wait for the right conditions to germinate. This often occurs...
following a course of antibiotic treatment, which can disturb the normal balance of gut flora, suppressing bacteria that are usually toxic to \textit{C. difficile}.

Upon infection, \textit{C. difficile} bacteria colonize the large intestine and produce at least two well-characterized toxins, simply called toxin A and toxin B, which attack the lining of the colon, causing abdominal pain and diarrhea. (See figure on opposite page.) A newly emerged pathogenic type of \textit{C. difficile}, known as 027/NAP-1/BI, \textbf{currently dominates the US landscape}. It produces more robust amounts of toxins A and B compared to other strains, which destroy the epithelial cells lining the intestine by interfering with the cell structure. Not surprisingly, the host responds by producing antibodies that recognize and neutralize the toxins, as well as cytokines and other inflammatory molecules to eliminate the offending toxins and bacteria. However, the inflammation that results can cause further damage to the epithelial cells, which normally form a gastrointestinal barrier, resulting in passive leakage and active transport of watery fluids into the intestine. This fluid cannot be reabsorbed by the damaged cells, and diarrhea results. As the immune battle continues, \textit{cellular debris from dead epithelium, immune cells, and bacteria accumulates along the colon wall, creating patches of a pseudomembrane that prevent the flow of fluids that usually washes out the pathogens}.

Additionally, many 027/NAP-1/BI strains of \textit{C. difficile} produce more spores, which can contribute to the load of bacteria in the bowel of the patient and subsequently of spores in the environment, where they are passed onto other individuals. These so-called hypervirulent \textit{C. difficile} strains are also hard to eradicate because highly conserved "sticky" surface proteins and other factors help them attach to gut surfaces. (See figure on opposite page.) Taken together, the robust production of two highly effective toxins, more spores, and multiple bacterial surface proteins that help \textit{C. difficile} persist make this new "superbug" a formidable adversary that calls for creative new therapies and a rethinking of traditional clinical treatments.

\textbf{New approaches for an old disease}

The improved management of CDI has been a top priority for pharmaceutical and biotech companies over the past decade. Currently, oral vancomycin (Vancocin) is still the only one drug approved by the Food and Drug Administration (FDA) for the treatment of CDI, though doctors usually first prescribe the equally well-established antibiotic metronidazole (Flagyl). Not only has the overall incidence of CDI risen, but as many as 40 percent of CDI patients will experience an acute recurrence of the infection within a month of initial treatment with one of these two traditional antibiotics. This combination of the increasing threat of infection and the persistent risk of recurrence has prompted some companies to seek alternative treatments for the pathogen.
A new antibiotic called **fidaxomicin that inhibits the enzyme RNA polymerase**, produced by San Diego-based Optimer Pharmaceuticals, Inc., is in the late stages of development. This drug showed clinical **cure rates of approximately 90 percent** (comparable to vancomycin), and significantly reduced recurrence rates—by 47 percent compared to vancomycin—when given twice daily to more than 1,100 patients in two Phase III clinical trials. Furthermore, fidaxomicin has a narrower spectrum of activity than vancomycin and metronidazole, meaning it is less likely to disturb the gut bacteria which normally help prevent invaders such as *C. difficile* from flourishing. Indeed, fidaxomicin has been shown to have a much muted effect on host flora. The drug, which last month received a unanimous recommendation for approval by an FDA advisory committee, was under review at the US agency and the European Medicines Agency when this article went to press. (Disclosure: Glenn S. Tillotson currently works for Optimer Pharmaceuticals, Inc.)

Ramoplanin, an antibiotic that blocks bacterial cell wall synthesis, which is being developed by Florida–based Nanotherapeutics and is slated to begin Phase III trials later this year; and Massachusetts–based Cubist Pharmaceuticals’ drug CB-183,315, which disrupts the bacterial cell membrane function and is currently in Phase II clinical testing.

Another potential therapy for CDI takes a step outside the box of traditional medicine. Known as **fecal bacteriotherapy**, or fecal transplants, it involves the creation of a saline-diluted solution of fecal matter from a healthy donor, which is introduced into a CDI patient’s gastrointestinal tract using a catheter or enema. Based on reestablishing a normal, healthy gut flora, whose disturbance often allows the flourishing of *C. difficile*, the treatment has been used sporadically in North America for the last few decades. Recently, however, it has begun to gain acceptance among clinicians and patients, and a 2009 review of 100 Scandinavian cases reported an 89 percent cure rate among CDI patients. Last October, epidemiologist Susy Hota of Toronto General Hospital began recruiting patients for the first North American randomized, controlled trial of the procedure, in combination with a 2-week regimen of oral vancomycin.

While these drugs and therapies hold promise as treatments for killing the bacteria after infection takes hold, other approaches are being developed to help protect at-risk patients before infection even begins. It is often flaws or weaknesses in the host’s immune system that enable *C. difficile* to become established more easily in the gut. As people age, their ability to make sufficient or appropriate antibodies goes down, which allows pathogens such as *C. difficile* to more easily evade the immune response. As the average age of CDI patients is more than 65 years, approaches that bolster immune function are being investigated to help quell the escalation in CDI.

Until recently, researchers did not know how to build a vaccine that would effectively target *C. difficile*. Rather than target the bacterium itself, researchers recognized that the body’s ability to protect against toxins A and B was of paramount importance in the fight, although the production of antibodies that block the adherence of *C. difficile* to the colon wall in the first place would be even better. There are now at least three approaches that aim to arm the immune system to fight CDI at various stages of the infection.
One such therapy is a vaccine being developed by Sanofi-Pasteur that uses neutralized forms of toxins A and B to bolster patients’ ability to make immunoglobulins that bind to and eliminate the disease-causing toxins. Phase I studies have shown that this vaccine, composed of a proprietary ratio of the modified toxins, was well tolerated and resulted in increased production of antibodies specific to the two toxins in healthy participants; however, the response rate was lower in those over 70 years old compared with those aged 25 years. The vaccine is currently being tested for the prevention of CDI recurrence in a Phase II trial in the United Kingdom and the United States. Last November, shortly after the FDA granted the vaccine a fast-track designation to expedite its development, the vaccine maker announced the initiation of a second Phase II trial—this one for primary prevention of CDI in at-risk individuals in the United States.

Merck & Co. also has a potential CDI treatment in its pipeline—a monoclonal antibody called MK-3415A that similarly targets toxins A and B. Last year, the pharmaceutical company reported that recurrence rates dropped by up to 72 percent in a Phase II trial of patients also taking metronidazole or vancomycin. Based on those results, Merck had planned to follow up with Phase III studies “in the near term,” according to a company spokesperson, but has currently put the program on hold “in view of ongoing interactions with regulatory authorities.”

A third alternative approach to managing CDI is to prevent the pathogenic strain of C. difficile from colonizing the bowel in the first place—a strategy that should subsequently thwart the production of toxins and spores. Previous studies in hamsters showed that infection with strains of C. difficile that do not produce the two toxins, but in all other ways resemble the pathogenic C. difficile, can protect against further infection. Because these harmless bacteria presumably attach to the same bowel sites as the dangerous bacteria, they block all points of contact for the virulent variety. ViroPharma Incorporated has partnered with Dr. Dale Gerding, an infectious disease physician at Hines VA Hospital in Chicago, to evaluate this biotherapeutic approach. Phase I data suggest that this nontoxicogenic C. difficile strain is well tolerated and colonizes the bowel of healthy volunteers, and the company plans to begin a Phase II trial this year. (Disclosure: Glenn S. Tillotson used to work for ViroPharma Incorporated.)

Rethinking CDI

Few other infections have been the subject of so many varied therapeutic approaches. Those currently in development for the treatment of CDI will no doubt be key to beating the newly emerging superstrains of C. difficile. In addition, the use of new patient assessments that assist in selecting the right therapy for the right patient is of paramount importance for reducing disease recurrence.

In the United States, recurrent C. difficile infections may cost nearly $10 billion in excess hospital expenses each year.

Currently, doctors treat CDI patients on the basis of disease severity at the time the patient is seen, as per clinical guidelines, and prescribe either vancomycin or metronidazole, depending on the early signs and symptoms. But immediate clinical outcome is not always indicative of the long-term consequences of recurrent infections. Recent studies suggest that there may be clinical and historical risk factors that are related to a higher incidence of recurrence, including age, prior CDI, concomitant antibiotics, renal failure, and immunocompromised status. Elderly patients, for example, are more likely to have had recent antibiotics for unrelated infections, which can decrease host defenses and perturb the normal gut flora, reducing populations of C. difficile’s inhibitors and competitors in the gastrointestinal tract. Other age-related diseases, such as cancer, can also adversely affect host defenses, thus reducing the patient’s ability to fight off invaders, and often require therapies that disrupt the gut flora. Prior infection by C. difficile may also lead to an increased risk of recurrence because of residual spores left behind in the bowel, where they await the right environment for regermination. It is the recurrence of CDI that presents a significant burden to health care systems and patients. An 8-year-old estimate assesses the annual excess hospital costs in the United States at $3.2 billion, and the costs now could be as high as $9.55 billion annually.

Almost a century ago Paul Ehrlich, the grandfather of chemotherapy, presciently warned of the emergence of organisms which would thwart our best medical efforts by developing means of resistance unless we “frapper fort et frapper vite,” roughly translated as “hit hard and hit fast.” When dealing with CDI, we must embrace this edict by choosing the right weapon for the right patient at the right time. Otherwise, Ehrlich’s predictions will continue to come true.

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VA Healthcare System. The authors wish to thank Joni Tillotson, a biology undergraduate student at Immaculata University, for her manuscript research and database compilation.

References:
11. D. Crook et al., “Efficacy and safety of fidaxomicin (FDX) vs vancomycin (VAN) in Clostridium difficile infection (CDI) in 2 randomized controlled trials (RCT) with 1105 patients” IDSA, Abstract 1417, 2010.

Stay away from hospitals
by anonymous poster, [Comment posted 2011-05-18 16:44:22]
Great article. Stay away from hospitals. Maybe California beaches too. Edo, can you name the 17 at risk beaches? Or would that be telling?
Levaquin brought it on
by anonymous poster, [Comment posted 2011-05-18 14:08:24]
Try the first line of medicine, Flagyl along with Floraster. The antibiotic knocks out the DCI and the Floraster displaces the infectious remnants. This followed with probiotics and yogurt to help your gut flora and fauna to repopulate. Healthy gut bacteria is good.
Immediate action needed.
by Akin Olagoke Ogunleye, [Comment posted 2011-05-07 15:48:10]
Clostridium difficile’s lethal tendencies should be stopped immediately. This can be done by developing very strong antibiotics that the bacterium cannot easily resist. The Research and Development units in leading pharmaceutical companies and pharmaceutical research institutes in the United States and elsewhere across the world should be of help in this regard.
C-Diff
by anonymous poster, [Comment posted 2011-05-06 17:32:26]
C-Diff is being used as a get rich scheme by doctors, especially with geriatrics. Patients induct C-Diff in hospitals, then are sent to nursing homes for “rehabilitation” where they are fed sleeping pills until the C-Diff becomes nearly irreversible. Then surgeons are paid to remove bowels and limbs.
Have you looked
by Lon Jones, [Comment posted 2011-05-06 11:19:57]
C-Diff is an increasingly complex problem because of our increased use of antibiotics that opens the doors for this opportunistic bug. Over ten years ago Paul Naaber showed that xylitol, a food sweetener, greatly decreases the adherence of C dif to gut like cells. Since significant amounts of xylitol cause diarrhea why not give enough to keep people loose and help wash out the bad bugs?
One reason why not is because that would be using a food as a “drug” and we don’t do things like that anymore thanks to the differentiation and regulations of the FDA. If it doesn’t make any money for the pharmaceutical industry we can’t use it. More info on the use of xylitol in this and other infections (from tooth decay to otitis) is found in our book, THE BOIDS AND THE BEES, published by the Institute for the Study of Coherence and Emergence, where they look for novel ways to treat complex problems—even those that don’t make a big profit.
CDI article response
by Carol Lackman-Smith, [Comment posted 2011-05-04 12:36:29]
Excellent article. In addition to a recent history of treatment with antibacterial therapy, I am wondering if the use of antacids might also provide ideal conditions for CDI, by preventing the first line defense of stomach acid in destroying the bug and its spores.
On the beach – C diff
by Edo McGowan, [Comment posted 2011-05-04 12:25:37]
Along the shoreline of California’s famous beaches, short shallow sewer plant outfalls discharge high volumes of presumably treated wastewater. Because the antiquated standards under which these plants operate, the water is hardly safe and with short shallow outfalls, the tides and currents bring this effluent right back to the beach and swimming area. C. diff easily survives sewer plant treatment and the spores are long lived in both surf and sand.
Of the 49 sewer outfalls along the California coast, 17 could be considered as short and shallow which may increase marine and beach sand contamination. Public beaches adjacent to these short shallow outfalls (SSO) may become reservoirs of pathogens, many of which are antibiotic resistant. Studies of beach sand in lake and marine systems have demonstrated contamination with a variety
of pathogens. Some studies specifically considered antibiotic resistant Staphylococcus aureus (MRSA) which now kills more Americans than AIDS, according to the CDC.

Beach goers who dug in the sand or covered themselves with sand were, in the following week or two, more likely to have diarrheal illnesses from a variety of organisms.

Beach sand, especially if it contains ground kelp, offers a good medium for the regrowth and maintenance of pathogens. Do SSO's augment the contamination of coastal beaches and are the bacteria likely to contain antibiotic resistant genetic material? An answer may be gained by tracking effluent released from SSO's. Pilot data indicate effluent is returned to the beach and near shore waters.

Sewer plants are a principal source for the generation and release of antibiotic resistant bacteria and their genetic material, per peer reviewed published facts for approximately 40 years. US/EPA also published on the topic in 1982. The California Department of Public Health and the Regional Water Quality Control Boards do not recognize this potentially dangerous situation and consequently have generated no standards for its control. CDC, US/EPA and IATFAR currently plan no research on the subject.

Dr Edo McGowan, Medical Geo-Hydrology

First-line treatment for HIV-2: superior outcomes seen with a boosted protease inhibitor

Michael Carter
Published: 31 May 2011
An antiretroviral combination based on a boosted protease inhibitor should be “considered as first-line ART for patients with HIV-2 infection”, an international team of investigators recommend in the May 15th edition of Clinical Infectious Diseases.

After twelve months of treatment, superior virological and immunological outcomes were seen in patients taking a combination of drugs that included a boosted protease inhibitor, compared to people treated with the recommended triple nucleoside reverse transcriptase inhibitor (NRTI) regimen.

“We showed better viral suppression and higher CD4 cell recovery associated with PI/r [protease inhibitor/ritonavir] than with a triple NRTI regimen,” write the investigators.

HIV-2 is found predominantly in western Africa; a small number of cases are diagnosed in Europe and North America each year.

HIV-2 infection is associated with slower disease progression, but its natural resistance profile means that fewer drugs are available for its treatment than HIV-1. In particular, drugs from the non-nucleoside reverse transcriptase inhibitor (NNRTI) class cannot be used.

Guidelines issued by the World Health Organization (WHO) in 2010 recommended that patients with HIV-2 should start antiretroviral therapy with a triple NRTI regimen. Protease inhibitor-based therapy is reserved for second-line treatment.

No randomised controlled trials have assessed the efficacy of specific combinations in patients with HIV-2. Nevertheless, some small observational studies have shown superior outcomes in patients treated with a ritonavir-boosted protease inhibitor.

Investigators from Europe, Gambia and North America therefore conducted an observational study to compare the effectiveness of triple NRTI and boosted-protease inhibitor regimens in HIV-2-infected people who started first-line treatment between 1998 and 2008.

A total of 170 patients were included in their analysis, 126 of whom (74%) received a boosted protease inhibitor.

The most commonly used triple NRTI regimen (72%) was 3TC, abacavir and AZT, and 61% of patients treated with a boosted protease inhibitor received lopinavir/ritonavir.

Changes in viral load and CD4 cell count were compared between the two regimens after three and twelve months of treatment.

Information was also gathered on the proportion of patients achieving “treatment success” after twelve months – defined as an undetectable viral load and an increase in CD4 cell count of at least 50 cells/mm³.

Viral load changes were comparable between the two combinations for the first three months of therapy. Thereafter, viral load remained low in patients who received a boosted protease inhibitor, but increased in patients treated with three NRTIs. After a year of treatment, patients taking a triple NRTI regimen had a higher viral load than those receiving a boosted protease inhibitor (4.0 vs 2.2 log₁₀ copies/ml; p = 0.005).

Analysis was then restricted to the subset of patients who had an undetectable viral load at the start of therapy. This showed that 8% of patients taking the triple NRTI regimen, compared to 3% of people taking a boosted protease inhibitor, had a detectable viral load at least once within the first twelve months of treatment.
Investigators turned their attention to immunological responses. As with viral load, these were comparable during the first three months of therapy. However, by month twelve, patients taking a ritonavir-boosted protease inhibitor had an average increase in their CD4 cell count of 76 cells/mm$^3$ compared to baseline, whereas individuals receiving three NRTIs had had an average fall of 60 cells/mm$^3$ compared to baseline ($p = 0.002$). This meant that CD4 cell counts at month twelve were significantly higher among patients taking a protease inhibitor (327 vs 191 cells/mm$^3$; $p = 0.001$).

Restricting analysis to patients with a baseline CD4 cell count above 200 cells/mm$^3$ showed similar results. After twelve months, patients taking a boosted protease inhibitor had an average CD4 cell count increase of 52 cells/mm$^3$, compared to a fall of 99 cells/mm$^3$ among people taking three NRTIs ($p = 0.02$). A similar trend was also present for patients with a baseline CD4 cell count below 200 cells/mm$^3$.

A sensitivity analysis that involved the 75% of patients taking currently recommended regimens showed superior virological and immunological outcomes among the people receiving a boosted protease inhibitor.

The investigators then assessed the proportion of patients who had a successful response to treatment. They found that 55% of patients taking a boosted protease inhibitor had this outcome, compared to just 10% of individuals treated with three NRTIs (difference, $p = 0.003$).

HIV-2’s natural pattern of resistance could explain the poorer responses seen in patients treated with three NRTIs, the investigators suggest.

None of the patients died, and the proportion developing a new AIDS-defining illness was low and did not differ significantly between the regimens.

“A combined end point reflecting successful clinical, therapeutic, virological and immunological measurements at month 12 showed superiority of PI/r over triple NRTI regimens,” comment the investigators.

They call for “further research... to evaluate the optimal cART regimen for treatment-naïve patients with earlier HIV-2-infection, at best through a randomized controlled trial”.

Reference


Long-term CD4 cell gains on treatment weaker in over-50s

Michael Carter
Published: 31 May 2011

US investigators have found people with HIV aged 50 and over have weaker immune restoration after starting antiretroviral treatment, and recommend that earlier treatment should be a priority in this group.

The study, published in the online edition of the Journal of Acquired Immune Deficiency Syndromes, also showed that the majority of patients had a CD4 cell count above 500 cells/mm$^3$ after five or more years of therapy and that 75% of individuals had an undetectable viral load.

Combination antiretroviral therapy became available in 1996 and rapidly transformed the prognosis of patients with HIV. However, published data examining the long-term effectiveness of such treatment is currently limited.

Therefore investigators from the Multicenter AIDS Cohort Study (MACS) monitored the CD4 cell counts and viral load of 614 HIV-positive gay men who had been taking potent antiretroviral therapy for between five and twelve years.

The investigators were especially eager to see if any factors were associated with longer-term outcomes, and hypothesised that age, and HIV disease stage before the initiation of therapy, as well as CD4 cell count and viral load during the first five years of treatment, would affect immunological and virological responses in the longer-term.

At the time HIV therapy was started, 47% of men were aged under 40 and 12% were aged over 50. A total of 4431 CD4 cell counts and viral load measurements were obtained from patients between years five and twelve of treatment.

Just over half (53%) the patients were taking therapy based on a protease inhibitor, and 70% of these individuals were treated with a ritonavir-boosted drug. Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based treatment was taken by 42% of individuals, with efavirenz (Sustiva) the most widely used.
drug (70%). A small proportion of patients (5%) were treated with a triple nucleoside reverse transcriptase inhibitor (NRTI) combination, a regimen which is now considered suboptimal.

Median CD4 cell count five to twelve years after starting therapy was 585 cells/mm$^3$.

In the first five years of therapy, significant increases in CD4 cell count were observed regardless of baseline CD4 cell count. However, CD4 cell counts stabilised after five years for patients who initiated therapy when their CD4 cell count was in the region of 350 cells/mm$^3$. There continued to be modest increases for people who started treatment with weaker immune systems.

Factors associated with poorer CD4 cell count gains after five years were a lower baseline CD4 cell count (p < 0.01), and co-infection with hepatitis B virus (p = 0.01).

Patients who had an undetectable viral load for at least 50% of the first five years of therapy had higher CD4 cell counts in the longer term (p < 0.01), as did individuals who remained on their first or second combination of drugs (p = 0.03).

Age at the initiation of HIV therapy also predicted longer-term outcomes. The mean CD4 cell count after five years of therapy was significantly lower for men who started treatment when they were aged 50 or over, compared to people who started treatment when they were aged under 40.

Younger men who started therapy when their CD4 cell count was in the region of 201 to 350 cells/mm$^3$ had a mean CD4 cell count of 670 cells/mm$^3$ after ten or more years of treatment.

In contrast, the mean CD4 cell count at this time point for the over 50s who initiated therapy with a similar count was 578 cells/mm$^3$, a significant difference (p < 0.01).

To achieve a similar long-term CD4 cell count as the under 40s, older patients would have needed to start therapy when their CD4 cell count was above 350 cells/mm$^3$.

“Our data support using age in the guidelines for initiating HAART [highly active antiretroviral therapy], such that persons who are older than 50 years should start treatment at higher CD4 counts,” write the authors.

Investigators also found that long-term outcomes were associated with total lymphocyte count. A count above 1200 cells/mm$^3$ at the time HIV therapy was started was associated with a significantly higher CD4 cell count after five years of treatment (p < 0.01).

“This finding supports the inclusion of TLC [total lymphocyte count] in HIV treatment guidelines,” comment the investigators.

Overall, 78% of viral load measurements obtained after five years of therapy were undetectable. Viral load in the first five years predicted subsequent outcomes, and virological control was significantly better in the long term for patients who were undetectable in this period (p < 0.01).

Switching treatment on two or more occasions was associated with poorer control of viral load in the longer term (p = 0.06).

Unsurprisingly, individuals who reported 100% adherence had good control of virus after year five.

“In this study, several factors were found to be associated with lower CD4 cell counts in men who received HAART for 5-12 years. Important modifiable factors were older age and lower CD4 cell count at the time of HAART initiation,” comment the researchers.

Nevertheless, they are encouraged by their overall findings, writing “this study shows that the effectiveness of HAART persists for up to 12 years”.

Reference

Church reiterates opposition on condoms to prevent HIV
Published: May 30, 2011

The Church has reiterated its opposition to condoms in the fight against HIV, again labelling them an ineffective prevention tool that encourages immoral behaviour, reports PBS NewsHour.

An AIDS conference hosted at the Vatican over the weekend quickly stamped out any lingering speculation that the Church might shift or broaden its policy against use of condoms to protect from HIV, the report added.

Instead, Vatican officials hailed recent findings that AIDS medications can be highly effective in preventing transmission and called for a change in “amoral sexual attitudes” that contribute to the spread of HIV.

The concept of using HIV medications as prevention offers particular appeal because it could be used within a marriage, without violating the tenet that the act of sex be “open to life.”
The AIDS conference was originally called in the wake of confusion over a statement by Pope Benedict XVI in late 2010, which said that use of a condom by certain individuals, like a male HIV-positive prostitute, might be a "first step in the direction of a moralisation, a first assumption of responsibility."

Some AIDS advocates read the words as a potential loosening of the Church’s long-held stance against condoms, which are "the single, most efficient, available technology to reduce the sexual transmission of HIV," according to UNAIDS.

Appearing at the conference Saturday, the head of UNAIDS Michel Sidibe echoed some of the disconnect when he praised the Pope’s earlier statement on the potential use of condoms for HIV.

"This is very important," Sidibe said. "This has helped me to understand his position better and has opened up a new space for dialogue."

"The truth is a condom is seen as something illicit because it goes against the Christian marriage," said Monseigneur Jacques Suaudeau, from the Pontifical Council for Health Care Workers. "People thought they could continue with their lifestyle thanks to the use of condoms. ... To many it was simply a way to continue to be totally irresponsible."

**UNAIDS to Vatican: Pope’s HIV-Condom View Helpful**

Associated Press, (05.28.2011) Nicole Winfield

At a Roman Catholic Church-sponsored conference on HIV prevention and care Saturday in Vatican City, the head of UNAIDS told attendees condoms are “integral and essential” in the fight against AIDS.

The Catholic Church does not support condom use, as part of its longstanding opposition against artificial contraception. But in a book published last year, “Light of the World,” Pope Benedict XVI said that a male prostitute who intends to use a condom could be taking a greater step toward responsibility by protecting the welfare of his partner.

“This is very important,” said UNAIDS Executive Director Dr. Michel Sidibe. “This has helped me to understand his position better and has opened up a new space for dialogue.”

Sidibe noted that the AIDS community and the church have been guilty of “talking over” one another and not working together. Benedict's statements open up the possibility for greater cooperation, he said, particularly in expanding access to antiretroviral treatment for the world’s poor. “Yes, there are areas where we disagree and we must continue to listen, to reflect and to talk together about them. But there are many more areas where we share common cause,” he said.

The fact that Sidibe was asked to speak is significant, given that the Vatican typically invites only like-minded outsiders to its conferences. Vatican officials, however, did not reference Benedict’s remarks on condoms. Monsignor Zygmunt Zimowski, head of the Pontifical Council for Health Care Workers, which hosted the conference, echoed Pope John Paul II and talked of the “crisis of values” behind the HIV/AIDS epidemic.

**Israeli study may point to the future of the HIV epidemic in men who have sex with men**

Over the past decade across high-income countries such as Canada and Australia and regions such as Western Europe an unexpected and disturbing trend has emerged—an increase in syphilis and HIV infections among men who have sex with men (MSM). Now researchers in Israel have found similar trends in HIV in that country. Furthermore, researchers there have found another troubling trend: A significant proportion (about 30%) of MSM newly infected with HIV have strains of this virus that are resistant to some anti-HIV therapies.

The Israeli report, published in the June 1, 2011 issue of the journal *Clinical Infectious Diseases* has incited an editorial to accompany it that calls out for concerted action to help communities of MSM become more resilient so that they can re-embrace safer-sex behaviours and help reduce the spread of HIV. The editorial cautions against the incorrect assumption made by some MSM that use of potent anti-HIV therapy, commonly called HAART or ART, will render them or their partners sexually non-infectious.

**Study details**

Researchers in Israel at several infectious disease clinics, public health departments and research centres collaborated on a large study to assess changes in behaviour that might help to explain the accelerating spread of HIV among MSM in recent years.

The study was made easier to conduct in part because in 1986 Israeli authorities established a centralized national HIV registry and National HIV Reference Laboratory (NHRL). In Israel, all doctors and laboratories are required to report details of newly diagnosed cases of HIV to the registry. The NHRL
confirms HIV infection in the blood samples it receives. It also conducts molecular analysis for strains of HIV that may be resistant to treatment and to monitor the evolution of the virus.

**Results**

By the end of 2009, there were 6,250 HIV-positive people in Israel, including 3,800 men over the age of 15. Our report focuses on MSM.

The proportion of MSM among all people in Israel newly diagnosed with HIV infection at different points in time was as follows:

- late 1980s – 38%
- 1990s – 7%
- 2009 – 35%

Most infected MSM (70%) were born in Israel and had a strain or subtype of HIV called subtype B. This strain of HIV is relatively common in North America, Australia, Japan and Western Europe. Based on its research and other findings, the team made this statement:

“The MSM epidemic in Israel is essentially homegrown and factors such as tourism and immigration do not significantly affect this conclusion.”

**Trends in recent HIV infection**

The study team noticed a trend: A significant proportion of MSM newly diagnosed with HIV infection was seen in recent years. Many of these cases were diagnosed just before or during HIV seroconversion (the period when antibodies to HIV develop), when participants had symptoms of initial HIV infection and with the use of tests for HIV’s genetic material or viral proteins that are detectable before antibodies develop. For instance, between 1996 and 2005, about 4% of MSM diagnosed with HIV were recently infected. Between the years 2007 and 2009, this proportion rose to 14%. In one clinic in Tel Aviv, the proportion was even greater, reaching 28% between 2007 and 2009.

**Syphilis**

In general, among men newly diagnosed with HIV infection, cases of co-infection with syphilis increased after 2005. Although cases of co-infection fell in 2009, they were still higher than in 2005.

**HIV resistance to treatment**

By the end of 2009, researchers had conducted molecular analyses of HIV isolated from 884 men before they had received any treatment. The researchers sought mutations in HIV’s genetic material that would allow the virus to evade the effect of anti-HIV drugs. Such changes to HIV’s genetic material are called major mutations. The proportion of MSM infected with mutations to HIV in different periods was as follows:

- 1990s – 20%
- early 2000s – 5%
- 2007 to 2009 – 29%

That nearly 30% of newly infected MSM in the recent era carry major resistance mutations to treatment is disturbing. However, given the increase in unprotected sex among MSM and outbreaks of sexually transmitted infections (STIs), perhaps this result should not be surprising. Using complex mathematical models and high-performance computers, Australian scientists have recently predicted that transmission of drug-resistant virus would become a common feature of the HIV epidemic among MSM.

The results of the molecular analysis done by Israeli researchers revealed that many newly infected MSM with drug-resistant virus would be unlikely to benefit from commonly used and less-expensive treatments such as efavirenz (Sustiva, Stocrin and in Atripla) and nevirapine (Viramune). Moreover, such mutations can persist for many years, reducing future treatment options.

**Subtypes**

According to the research team, “Until recently, all MSM had subtype B [of HIV], but recently, MSM carrying [subtypes] A/AE and C viruses were indentified. The greater variety suggests risky sexual behaviour with larger groups of sex partners.”

**Aware of risks but...**

The researchers stated that “the higher percentage of MSM who received [an HIV] diagnosis relatively soon after being infected and even [just] before seroconversion suggests also that many MSM may be aware of having practiced risky sexual contact and/or are sensitive to initial signs of infection. Although such awareness did not prevent their risky behaviour, they appear to seek immediate clarification of their infection status and medical advice.”
Early detection and yet transmission still occurs
The study team noted: “Detection of HIV positivity at an earlier stage after infection, as observed, should tend to diminish the rate of virus transmission among MSM, but evidently, this was not enough to reverse present trends.”

Explaining the reemergence of HIV
An editorial that accompanied the Israeli research was published in the journal Clinical Infectious Diseases by Boston-based HIV researcher Kenneth Mayer, MD. He observed that before HAART became available in 1996, safer sex was widely encouraged among MSM because their communities were “saturated with reminders of the consequences of unprotected sex.” By encouraging safer sex, these communities helped to reduce the spread of HIV among MSM in urban areas of high-income countries.

Dr. Mayer adds that as HAART decreased the “visual stigmata” of the HIV epidemic and transformed it into “a chronic, serious but manageable infection, the tangible reminders of AIDS disappeared and increasing risk behaviour among MSM reemerged in conjunction with this ‘therapeutic optimism’.”

Can treatment as prevention work for MSM?
The editorial notes that the findings from Israel “call into question some of the recent optimism about ‘treatment as prevention [TASP].’” Proponents of TASP suggest that if efforts were greatly expanded to test communities or populations for HIV infection and then offer prompt treatment, the AIDS epidemic could be halted. But the data from Israel suggest that some MSM are engaging in high-risk behaviour. This, coupled with either non-adherence to HAART or inflammation of the genital tract (which amplifies HIV replication) perhaps caused by syphilis, likely results in the transmission of drug-resistant HIV.

Non-adherence or co-infection with STIs may not be the only reason for drug-resistant HIV transmission in the Israeli study. Working independently, two teams of Canadian scientists in Ottawa and Toronto have found that MSM who do not have STIs and who are adherent to HAART and have undetectable levels of HIV in their blood can have, from time to time, detectable levels of HIV in their semen.

Beyond therapeutic optimism
Dr. Mayer states that therapeutic optimism can only partially explain the reemergence of the HIV pandemic among MSM. Other research suggests that depression and substance use may also play a role. Additionally, Dr. Mayer says, “early life experiences, ranging from sexual abuse to homophobic violence” may result in decreased self-esteem and the reduced ability of MSM to protect themselves from harmful behaviours.

A warning
Dr. Mayer suggests that the situation in Israel may be an early picture of the eventual transformation of the HIV epidemic among MSM in other high-income countries. Based on the Israeli report, he offers this important warning:

“MSM should not assume that their partner is HIV-uninfected, and if he is infected, it is unwise to assume that his medication will make him noninfectious.”

Reducing new infections in MSM
The editorial suggests that community members, clinicians and public health authorities enrich ideas of “test and treat” with the promotion of human rights for sexual and gender minorities, intensified community education, culturally appropriate care for MSM and attention to the consequences of traumatic psychological events. In this way, according to Dr. Mayer, we can one day halt the spread of HIV among MSM. He states that by not taking these actions, “a future with increased transmission of resistant HIV is guaranteed.”

References:
Gay sex became legal in India two years ago, but attitudes change slowly

For most gay men in Hyderabad, Andhra Pradesh, the law change has made little obvious difference, but they do seem to be louder and prouder

Indian gay rights supporters at the Queer Azadi march in Mumbai, August 2009. At least 2,000 people took part in the pride march, only weeks after the British colonial-era ban on sex between men was ended. Photograph: Sajjad Hussain/AFP/Getty Images

The day the high court in Delhi ruled that being gay was no longer a crime was the day that Krishna Gurram Kouda finally came out to his family.

Despite having set up a state-wide network for gay men in Andhra Pradesh, the 39-year-old had never told his relatives about his sexuality. "I live with my parents," he explains as the fan above whirs in an ineffectual attempt to stave off the 400 C Hyderabad heat. "I have a good relationship with my brothers and their children." He looks at me. "I thought they would accept me," he pauses, "but I was a little afraid."

I first met Kouda in 2008 when I was reporting on how discrimination puts gay men at greater risk of HIV in Andhra Pradesh (which has one of India's highest rates of the virus) for the Guardian's international development journalism competition. At that time, section 377 of the Indian penal code made gay sex illegal, and strong social stigma drove gay men underground. Now the law has changed, I wanted to know whether their lives had also altered course.

For Krishna, the answer is yes. On the day of decriminalisation – 2 July 2009 – Krishna went public, spending hours on local TV and radio, talking about gay issues and rebutting religious leaders. When he got home at 10 o'clock that night, his mother and brother congratulated him. "You speak about your community's problems so well," they said, recognising for the first time that they knew he was gay. Since then, Krishna and Avinash, his partner of seven years, have received joint invitations to family parties and an annual couples-only Puja [prayer].

But for most of the gay men I met, decriminalisation had made little obvious difference. Hyderabad, the capital of Andhra Pradesh, is 1,500km and a cultural leap away from middle-class activism in Delhi, where the case was won.
"There is no change," says Satish, an outreach worker at a drop-in centre for men who have sex with men in Secunderabad, Hyderabad’s twin city. "Same harassment by police, same harassment by society, same harassment by goondas [thugs]."

"It's like this," another chips in. "Section 377" – he kisses his teeth and flicks his hand dismissively "only high level people who are going on websites and reading the paper know about that. Not the medium-class people, not the lower class."

Only a week earlier, a 30-year-old transgender sex worker nick-named Charmi was badly beaten by the police at a cruising point in Secunderabad. A distant legal change is not enough to stop rank-and-file officers beating gay and transgender people who they call "bad people" and robbers.

Nor is it enough to counter social and economic pressures facing poor men: "The really bad situation is facing the low-income people," says Krishna. "They depend on their family financially, emotionally. They can't say, 'I am gay, I don't want to marry.' They have nowhere to go."

HIV rates among gay men remain high. Although data collection is problematic, one study indicates that one-fifth of men who have sex with men in Andhra Pradesh were HIV positive in 2009/10, compared with one-sixth in 2007.

The legal change may have had limited direct impact, but life is by no means the same as it was three years ago. Krishna’s organisation, Suraksha Society, reports that beatings, rapes and thefts by the police have reduced dramatically in the areas where it works.

This is because Suraksha members now make weekly visits to every police station in Hyderabad, and run monthly sex and sexuality workshops with the police.

"One day we asked – why are we blaming the police? How many times have we tried to explain our sexuality to them?" says Krishna. "When we told them about our struggles, most were very impressed. They said, really, we didn't know this kind of thing, we thought you were bad people only." The Suraksha men now have such a good rapport with the police that they distribute condoms to the cops and run HIV testing clinics for them at police stations.

Hyderabad also had its first gay pride march, a 3,000-strong rally in November 2009 called Melukolupu (awakening). The media is becoming more sensitive, and when one channel, TV9 Telugu, exposed local gay men on the dating site PlanetRomeo.com, there were protests and the channel was forced to apologise.

The legal change has brought no revolution in Hyderabad, and stubborn economic and social blocks stand in the way of greater freedom for many. But, in some ways, things are moving fast. Sitting in Krishna’s office as the stiflingly hot afternoon draws to a close, phones ring and legal documents are swished back and forth, and I sense that the men of Suraksha have become louder and prouder.

"Earlier we talked 99% about condoms and HIV. But this is only one part of our lives, a small part," says Krishna. "We also need rights and acceptance, and that's what we are fighting for."
Adshel Gives in to Homophobic Pressure and Removes Gay Safe Sex Advertisements

Adshel, the company that provides advertising in bus shelters around Brisbane, has today given in to pressure from the Australian Christian Lobby and removed a safe sex campaign featuring a gay male couple.

Adshel, Goa Billboards (where the advert is also placed) and the Advertising Standards Bureau have received complaints from a clearly orchestrated campaign from a well-organised minority to have the advertisements removed.

The advert has been released by the Queensland Association for Healthy Communities* (‘Healthy Communities’) as part of our Queensland Government funded HIV prevention and sexual health promotion work with gay men.

The ‘Rip & Roll’ advert features a gay male couple (fully clothed) in an affectionate embrace holding an unopened condom packet. The campaign logo “Rip & Roll” is featured with an unbranded condom in its packet. It is accompanied with the strap-line ‘A safe sex message from Healthy Communities’ and provides our web address and 1800 line.

“We are deeply disappointed by the behaviour of Adshel in removing the advertisements, without even notifying us and without proper reason” said Paul Martin, Executive Director of Healthy Communities.

“The advert is in no way explicit or offensive to the average Queenslander. The complaints claim that depictions of gay people and discussion of sexual health are not appropriate for the general community. We reject these claims outright.”

“2010 saw the highest number of people diagnosed with HIV than at any time since testing began in the mid 1980s. 65% of these diagnoses are among gay men. Now, more than ever, it is important that we get the safe sex message out to Queenslanders, particularly gay men, wherever they may be.”

“The advertisement is quite conservative when compared with other public advertisements for a range of commercial products and previous sexual health campaigns by the Australian and Queensland Governments.”

“The Australian Christian Lobby has used homophobia dressed up as protecting children to have an important public education campaign removed. ACL’s Queensland Director Wendy Francis has previously been criticised and forced to apologise for sending out a homophobic tweet likening gay marriage to ‘legalising child abuse’. They are now trying have gay people erased from the public sphere.

ACT reaches out to men who bareback

NEWS / Outraged reaction appears on Facebook
Andrea Houston / Toronto / Friday, May 27, 2011

Rather than condemn barebacking, the AIDS Committee of Toronto (ACT) is offering harm reduction information in its condom kits.
ACT’s position is that condoms are always the best choice, says Andrew Brett, communications coordinator at ACT. Even so, it’s important to acknowledge the reality, which is that some people don’t use condoms.

“People will make their own choices about sex, so it’s best they have the tools to make sex safer,” he says.

The condom package reads, “It’s your choice. We recognize that sex is a spectrum of possibilities. From pig sex to vanilla. Barebacking to wrapped.”

One gay man who took a free condom from an ACT volunteer at the Inside Out Film Festival reacted later with anger on Facebook, calling the message “appalling” and “morally despicable.”

But there’s no point ignoring that barebacking exists, Brett says. It’s better to discuss it and raise awareness about all preventative strategies.

“People are going to have sex, and it’s their choice in whatever sex they have,” he says. “If someone is going to have bareback sex, then there’s nothing we can say that is going to stop them. We still have information for them to make it safer.”

Brett offers an example: using more lube reduces the likelihood of skin tears.

It’s a touchy issue, but at least people are talking, Brett says. The condom has opened the door to discuss sensitive issues.

“We recommend condom use. But we recognize the reality of our sex lives,” he says. “I’m glad it’s created an opportunity to have a discussion. We need to have discussions about what our sex lives actually are, and not pretend that everyone is always using a condom every single time.”

Todd Klinck, co-owner of Goodhandy’s, calls the campaign “smart” and says he has no problems with ACT’s decision to provide harm reduction information about barebacking. But, outside of the campaign, he worries that the subculture of barebacking is becoming “normalized,” especially by the porn industry. Klinck doesn’t want young people getting the idea that it’s socially acceptable.

“[Barebacking] exists yes, and we should talk about it, but we shouldn’t normalize it.”

That’s something he already sees happening. In porn, barebacking is very common.

“The number one porn is barebacking. Statistically, that’s what everyone wants to see.”

Brian Finch, founder and publisher of Positive Lite, sees many sides in this debate. Although he agrees with Brett that burying one's head in the sand contributes to the problem, he says, barebacking shouldn’t be promoted.
“There’s so much controversy when this comes up,” Finch says. “I fall alongside with ACT on this. We have to acknowledge it, but I have to say I’m a little surprised to see it there.”

The bigger problem, Finch says, is how messages about HIV prevention have changed over the past number of years. Media campaigns have increasingly targeted people’s bad behaviour, like “the sex police.”

At the same time, Finch says, context is everything. If the ACT condoms were distributed at a school, he may have a different opinion.

“That may not be such a great idea,” he says. “When you’re handing out condoms to teenagers, maybe not include that message.”

Brett says ACT stocks a wide range of condom packages tailored for each outreach venue and event. The package handed out at Inside Out, but was created in August 2010 for a discussion forum on “pig sex and how to make it safer.” Brett says each pack contains two condoms and two lubes. More than 60,000 packs were distributed since the launch of the campaign.

“These packs were so popular that we needed to print more,” he says.

Rui Pires, ACT's gay men's community education coordinator, says the condom packs were focus tested along with a few other packs with seven focus groups totally 62 gay and bisexual men.

“Not a single man indicated they thought these packs advocated unprotected sex. Pig sex has specific connotations for a small subculture of gay men. What those connotations can mean varies from person to person.”

If you must bareback, here’s some tips from ACT to make it safer:

- Make sure your partner is actually consenting (agreeing) to bareback sex: he shouldn’t be drunk or high, or in any other type of altered state that may prevent him from making a decision he wouldn’t normally make for himself.
- If you are HIV-positive, you should be aware of the legal obligations surrounding HIV disclosure (ie telling your HIV status).
- Use lots of water-based lube
- Avoid douching (washing inside the ass). Douching removes the natural protective membrane in the ass. If you still choose to douche, use warm water only.
- Urinate immediately after fucking. This can help to clean out the urethra (pee passage)
- Also, educate yourself on prevention. Poz guys are especially open to getting or passing on other sexually transmitted infections, like syphilis and hepatitis C. STIs are more difficult to treat if you are HIV-positive. They can also progress much quicker and increase the amount of HIV in a poz guy’s semen and other parts of the body.
- Drug resistance happens when HIV mutates so that specific HIV treatment drugs (or an entire class of drugs) become less effective.
- More questions? Contact ACT at 416-340-8484 or visit their website: www.actoronto.org

Home Is Where the HAART Is: An Examination of Factors Affecting Neighborhood Perceptions Among People with HIV/AIDS on Antiretroviral Therapy

AIDS Care Vol. 23; No. 2: P. 245-251, (02..2011) Krisztina Vasarhelyi; Eirikka K. Brandson; Alexis K. Palmer; Kimberly A. Fernandes; Wendy Zhang; David M. Moore; Julio S.G. Montaner; Robert S. Hogg

Among a population of patients receiving highly active antiretroviral therapy in British Columbia, the current research evaluated how neighborhood perceptions are influenced by socio-economic factors including food security and stable housing. “Understanding the neighborhood perceptions of individuals living with HIV in urban and nonurban areas may help identify potential barriers to uptake and effectiveness of therapy,” the authors wrote.

An interviewer-administered survey was used to document patients’ neighborhood perceptions, quality of life, and socio-demographic data. Previously defined scales were used to evaluate perceptions of neighborhood problems, neighborhood cohesion, and relative standard of living. Bivariate and multivariate analyses were applied to identify associations with neighborhood perceptions, food security and stable housing.

The analyses were based on 457 participants, of whom 133 (29 percent) were food secure and 297 (65 percent) had stable housing. The mean scores for perceptions of neighborhood problems and cohesion were 35 (IQR 15-58) and 57 (IQR 46-69), respectively.

“Being food secure and having stable housing was associated with a 9 percent and 11 percent decrease in perception of neighborhood problems, respectively, and a 6 percent increase in the perception of
neighborhood cohesion in both cases,” the authors concluded. “Food security and stable housing are related to neighborhood perceptions among individuals on HAART. The results point to potential targets for intervention, involving improvements to living conditions such as housing and food security, which may promote treatment success for HAART, especially in marginalized communities.”

**All in Your Head? Substantial Recovery Rate With Placebo Effect in Headache Treatment, Analysis Finds**

ScienceDaily (May 29, 2011) — Headache is a very common complaint, with over 90% of all persons experiencing a headache at some time in their lives. Headaches commonly are tension-type (TTH) or migraine. They have high socioeconomic impact and can disturb most daily activities. Treatments range from pharmacologic to behavioral interventions. In a study published online in the *Journal of Manipulative and Physiological Therapeutics*, a group of Dutch researchers analyzed 119 randomized controlled clinical trials (RCTs) and determined the magnitude of placebo effect and no treatment effect on headache recovery rate.

"Although the intention of control and placebo interventions in research studies is to be relatively ineffective, the question rises as to what factors might cause improvement seen in these groups," commented corresponding investigator Arianne P. Verhagen, PhD, Assistant Professor, Department of General Practice, Erasmus Medical Center, Rotterdam, The Netherlands. "The aim of this study was to analyze the observed effects in the 'no treatment' and placebo control groups in clinical trials with TTH and migraine patients."

In the headache clinical trials studied, the "no treatment" and placebo groups had a high overall recovery rate of 36%. Control groups in pharmacological trials showed a higher response rate than the behavioral (non-pharmacological) trials (38.5% vs. 15.0%). Patients had higher recovery rates in the acute treatments compared with the prophylactic treatments (39.6% vs. 32.8%). Knowing that a substantial portion of patients improve without treatment is important when considering the benefits and risks of daily headache treatment.

Pharmacological treatment typically starts when non-pharmacological treatments like lifestyle changes, relaxation therapy, cognitive therapy, and reassurance do not work. Many of the prescribed or over-the-counter medications, such as non-steroidal anti-inflammatory drugs (NSAIDs), may lead to adverse events and medication overuse headache. Considering the risks of adverse events, the authors recommend that "the prescription of medication needs to be carefully considered and evaluated with each individual patient. Because of the recovery results in 'no treatment' control groups in pharmacological trials, the question rises whether or not this way of prescription is always preferable over no treatment (wait and see) especially in the TTH population."

**Journal Reference:**