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New Delhi, July 4

India’s fundamental role in the global response to the HIV/AIDS epidemic came to the fore today with the UNAIDS chief giving the country’s robust pharmaceutical sector credit for improved global survival rates and treatment possibilities by meeting bulk of the global drug demand at phenomenally low costs. India exports drugs to 200 countries.

“Almost 6.6 million people living with HIV are on treatment today because India has produced high quality and low-cost generic drugs. Over 86 per cent of the positive people are accessing treatment globally because of India,” Michel Sidibe, Executive Director, UNAIDS, said.

He was speaking at the National Convention of parliamentarians, legislators, Zila Parishad chairpersons and mayors, which Prime Minister Manmohan Singh and UPA chairperson Sonia Gandhi attended to reiterate the country’s political commitment to reverse the epidemic. India currently has 24 lakh persons living with HIV.

Sidibe, who is in India close on the heels of the UN high level meet on HIV/AIDS where world leaders committed themselves to “zero new infections, zero discrimination and zero deaths due to AIDS” in June, went on to say that the world would not be able to realise its shared vision of zero infections without India’s leadership. “India’s role is critical; without its leadership, we can’t achieve the goal we have committed ourselves to,” he said. Elaborating on the impact of Indian drugs, Sidibe, who hails from Africa (which bears the highest burden of AIDS), said Africa had reduced new HIV infections by 33 per cent over the past decade and posted a 12-fold increase in persons living with HIV.

“This has happened because India made available cheap anti-retroviral drugs,” he said. Considering that 96 per cent HIV treatment cost around the world is met from donations outside of those countries, Sidibe has urged India not to buckle under pressure from developed countries that want to use TRIPS (Trade Related Aspects of Intellectual Property Rights) to patent HIV drugs, thus pushing up costs.
“India has to resist attempts of TRIPS being used to block its ability to produce cheap drugs that are saving people’s lives,” said the UNAIDS chief, triggering strong responses from Health Minister Ghulam Nabi Azad.

INTERVIEW—Millions will die if India stops AIDS drugs—U.N.
Tue Jul 5, 2011 12:05pm GMT
By Nita Bhalla
NEW DELHI, July 5 (Reuters) – Millions of people dependent on life-saving generic drugs to treat HIV/AIDS will die if India stops producing cheap drugs for the disease due to its trade deal with the European Union, the head of UNAIDS warned on Tuesday.

The EU and India are currently negotiating a free-trade agreement, which campaigners say will restrict India’s ability to produce anti-retroviral (ARV) drugs, preventing the world’s poor from accessing cheap drugs for their treatment.

"India should resist removing any flexibility because any trade agreement which could lead to India not being able to produce will be terrible for the rest of the world," said Michel Sidibe, executive director for the Joint United Nations Programme on HIV/AIDS (UNAIDS).

"Millions of people will die if India cannot produce and Africa will be the most affected. For me, it is an issue of life or death," he told Reuters in an interview, adding that about 86 percent of people on treatment were taking drugs made in India.

The EU-India trade deal includes measures that could delay or restrict competition from generic medicines by extending patent terms, requiring data exclusivity and tightening border enforcement rules.

Such moves could drive up prices for India's anti-retroviral treatments, limit dosage options and delay access to newer and better drugs, said a U.N. report in September last year.

Thirty years after the HIV/AIDS virus was first discovered, experts say while substantial progress has been made by the global community in stemming it, only a fraction of those living with the illness are on medication.

At a high level U.N. meeting last month, nations agreed on a set of ambitious targets to rid the world of disease, including scaling up the provision of generics to reach 15 million patients from six million by 2015.

The trade deal, Sidibe said, would reverse many of the gains made in improving the lives of the world’s poor.

"We have been fighting for so long to make sure that poor people could have access to treatment," he said. "For me, it will be the beginning of reversing all the gains we made on social justice and redistribution of opportunity."

Sidibe, a Mali national, said African leaders were asking India to really pay serious attention to any trade agreement which would block them to produce quality generic drugs for very poor people.

"It is not a rich pocket of people in the developed world who will be deprived of drugs, it will be the most needy, the most poor." (Editing by Yoko Nishikawa)

Chlamydia Trachomatis Infection Among Women Reporting Sexual Activity with Women Screened in Family Planning Clinics in the Pacific Northwest, 1997 to 2005
American Journal of Public Health Vol. 101; No. 7: P. 1284-1290, (07..2011) Devika Singh, MD, MPH; David N. Fine, PhD; Jeanne M. Marrazzo, MD, MPH

The authors sought to define positivity for Chlamydia trachomatis (CT) among women who have sex with women, “a population for which sparse data on this infection are available and for whom health disparities, including challenged access to comprehensive sexual and reproductive health services, have been reported.”

The team analyzed data from 9,358 visits to family planning clinics that included CT testing among women ages 15 to 24 whose reported sexual activities in the past year had been exclusively with women (WSW) or with men and women (WSMW) in the Region X Infertility Prevention Project. The characteristics of these patients were compared with women who reported sex with men only (WSM).

Among both WSW and WSMW, CT positivity was 7.1 percent, compared to 5.3 percent among WSM. Compared to WSM, WSW and WSMW more commonly reported behavioral risks. Risks for CT positivity were comparable across groups; these included younger age, nonwhite race, behavioral risks, and clinical signs.
“Higher [CT] positivity among women reporting same-sex sexual behavior supports investigation into potential explanatory factors, including sexual behaviors, biological susceptibility, routine [CT] screening disparities, sexual identity disclosure, and sexual network assessment,” the authors concluded.

Key Immune Substance Linked to Asthma, Study Finds
ScienceDaily (July 2, 2011) — Stanford University School of Medicine investigators have linked a master molecule of the immune system, gamma-interferon, to the pathology of asthma, in a study of mice. This somewhat surprising finding—the key immune molecule has often been assumed to steer the immune system in a different direction from the cluster of allergic disorders to which asthma belongs—could lead to new treatments for the disease.

Gamma interferon’s role in asthma has been fuzzy. High levels of this substance in children’s blood seem to be protective against the development of asthma. Yet high gamma-interferon concentrations are often found in severe asthmatics’ lungs. The new study, which will be published online July 1 in the Journal of Clinical Investigation, amasses several lines of evidence indicating that gamma-interferon may be contributing to the severity of asthma.

"People thought gamma-interferon might have something to do with driving asthma's pathology, but there wasn't a whole lot of corroborating evidence,” said the study’s senior author, Stephen Galli, MD, professor and chair of the Department of Pathology at Stanford medical school.

As many as 28 million people in the United States have asthma, whose prevalence has increased a great deal in the past few decades in developed countries. Asthma’s signature symptom, extreme difficulty in breathing, is accompanied by transient narrowing and long-term inflammation of the air passages and, with time, lasting and detrimental structural changes in the architecture of the lungs.

Gamma-interferon, a signaling molecule secreted by certain immune cells, mobilizes the immune system to fight infectious pathogens—or, inappropriately, to attack healthy tissues, resulting in autoimmune disease. Asthma has been thought to result from a quite different mode of immune-system response that battles multi-celled parasites such as intestinal worms, but can unfortunately also trigger allergic reactions.

Another prominent feature of asthma is local abundance and activation, in lung tissue, of immune cells called mast cells, along with increased numbers of other kinds of inflammatory cells. But mast cells appear to be particularly critical in the development of asthma. These cells carry, on their surfaces, outward-facing antibodies that, in some cases, bind to allergens such as cat dander, pollen or cockroach droppings. This spurs the mast cells to secrete substances that trigger an asthma attack.

Curiously, mast cells have receptors for gamma-interferon.

The researchers used a mouse model of asthma to pin down gamma-interferon’s role in that disease. Galli credits the study’s first author, Mang Yu, MD, PhD, a senior research scientist who works closely with Galli, with producing the animal model of asthma that was used in the study. Five years ago, Yu, Galli and their associates had reported on Yu’s then-new method for inducing asthma-like symptoms in ordinary, otherwise healthy mice in a study published in the same journal. The method involves repeatedly exposing the mice to a foreign substance over a period of 12 weeks.

In that 2006 study, the Stanford team employed both Yu’s asthma-inducing protocol and mast-cell-lacking mice—pioneered by Galli, a specialist in mast-cell biology, in the 1980s—to show that, as good as Yu's protocol may be at producing asthma-like features in normal mice, it loses its ability to do so in mast-cell-free mice, even after those mice are supplied with mast cells that have been genetically altered so that all of their antibody-like surface receptors are defective. Providing those same mast-cell-lacking mice with healthy mast cells completely restored the protocol's capacity to induce asthma-like features.

In the new study, a similar approach—providing mast-cell-deficient mice with mast cells whose surface receptors for gamma interferon had been knocked out—showed a roughly equivalent ability to negate Yu’s protocol's induction of asthma in the mice. Alternatively, giving fully functioning mast cells to such mice restored the protocol's power to trigger the asthma-associated symptoms and gene-activity level changes that normal mice develop under the regimen.

"This is potential important news, because it suggests that gamma-interferon might represent a therapeutic target," said Galli, who is also a professor of microbiology and immunology and the Mary Hewitt Loveless, MD Professor in the School of Medicine.

In addition to its discovery about gamma-interferon, the new study also further validated Yu’s mouse model. Working with PhD student Alexander Morgan under the direction of his adviser, associate professor of pediatrics and of computer science Atul Butte, MD, PhD, the researchers were able to...
reproduce in such mice not only the gross symptoms of asthma but also the overall patterns of changes in the activity of genes in lung tissue that typify people with asthma.

Still, Galli said, 'My MD doesn't stand for 'mouse doctor.' It stands for 'medical doctor.' And I recognize that human asthma is not necessarily the same as a mouse model of asthma, even a very good one like the one we’re using. In implicating gamma-interferon as one of the drivers of pathology in this mouse model of asthma, we’ve raised just one question, which is: 'Could this also be true in humans and, if so, might interfering with gamma-interferon be helpful in treating them?' Mang and I can work on mice until the cows come home, and we couldn't answer that question."

Galli added a further caveat. "Even if levels of gamma-interferon are high in patients with severe asthma, that doesn't necessarily mean that if you block gamma-interferon they're going to get better. That would have to be established in clinical tests of human patients”—a prospect that may not be all that remote.

"The reason severe asthma exists is that some people don't respond well to typical therapies," said Sally Wenzel, MD, director of the University of Pittsburgh Asthma Institute and a professor of medicine at that university, who has identified increased levels of gamma-interferon in the lungs of severe asthma patients. Wenzel, who is familiar with Galli's new study but did not participate in it, said that she and Galli intend to collaborate in further research "to see whether the findings he's observed in the mouse model actually apply to living, breathing, asthmatic human beings."

**Journal Reference:**
Mang Yu, Michael R. Eckart, Alexander A. Morgan, Kaori Mukai, Atul J. Butte, Mindy Tsai, Stephen J. Galli. **Identification of an IFN-γ/mast cell axis in a mouse model of chronic asthma.** *Journal of Clinical Investigation*, 2011; DOI: [10.1172/JCI43598](https://doi.org/10.1172/JCI43598)

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**Confirmatory viral load reduces HIV treatment switches fourfold in 6-country African study**

Carole Leach-Lemens  
**Published: 06 July 2011**

Targeted viral load testing to confirm treatment failure reduced unnecessary treatment regimen switches four-fold compared to clinical-immunological criteria alone (viral load <1000 copies/ml 12.4% and 46.9%, p<0.001, respectively) among 250 patients in six African countries according to Kim C.E. Sigaloff and colleagues in a cross sectional analysis of a multicentre prospective observational study published in the advance online edition of the *Journal of Acquired Immune Deficiency Syndromes.*

However, switching on the basis of confirmatory viral load testing did not reduce the risk of drug resistance.

Nucleoside reverse transcriptase inhibitor (NRTI)-associated cross resistance was seen in close to 50% (87) of the 183 specimens available for genotypic analysis and did not differ by the type of failure identification used (clinical-immunological failure alone or with the addition of targeted viral load testing).

NRTI cross-resistance and the accumulation of thymidine analogue mutations (TAMs) were both associated with length of time on ART and zidovudine (AZT) use; tenofovir (TDF) use was additionally linked to NRTI cross-resistance.

The presence of at least one clinically significant mutation in 88% after first-line failure suggests late failure detection, the authors noted.

Increased access to first-line antiretroviral treatment in sub-Saharan Africa over the past decade has shown good short-term results. Long-term follow-up remains limited. Treatment failure for some is inevitable, increasing the risk of HIV-related morbidity and mortality.

Recent World Health Organization (WHO) guidance supports the use of viral testing if feasible to improve identification of treatment failure. Financially and logistically this is impossible in most resource-poor settings. So reliance on clinical criteria and CD4 cell counts is the norm for clinicians to determine treatment failure and help guide switches to second-line regimens.

Studies have shown use of clinical and immunological criteria alone in African countries cannot accurately determine virological failure in first-line treatment.

WHO recommends a switch in treatment if the CD4 count falls by more than 50% from its previous peak level, or if the CD4 count falls to its pre-therapy baseline (or below); or if it persistently remains below 100 cells/mm³.

Immunological criteria for switching have been found to result in unnecessary switches to second-line treatment, however.
For example, a study conducted in Uganda found that only 18 of 125 immunological non-responders receiving antiretroviral treatment had a detectable viral load. The investigators noted that 107 patients would have switched treatment unnecessarily, at an extra cost of $75,000 a year for drugs alone. Incorrect diagnosis of treatment failure in the absence of a confirmatory viral load test leads to inappropriate switching to more expensive and toxic second-line regimens.

Late failure detection can result in considerable resistance to ARVs, notably cross-resistance within the NRTI drug class. This can then hamper the effectiveness of standard second-line regimens comprised of a dual backbone of NRTIs and ritonavir-based protease inhibitor (PI) prevalent in resource-poor settings. Benefit would derive primarily from the boosted PI so patients would essentially be getting monotherapy, so lowering the barrier of PI resistance.

The objective of the PharmAccess African Studies to Evaluate Resistance Monitoring (PASER-M) multicentre prospective observational study of HIV-infected adults who get ART at 13 clinical sites in Kenya, Nigeria, South Africa, Uganda, Zambia and Zimbabwe is to look at the consequences of the use of clinical immunological criteria to determine treatment failure and guide treatment switching.

The authors undertook a cross-sectional analysis to look at how frequently unnecessary changes to second-line regimens were made, the patterns of resistance that developed in those on failing first-line ART and the risk factors for the accumulation of NRTI-associated mutations.

Participants were included if switched to second-line ART regardless of criteria to determine failure. Comparisons were made according to clinical-immunological failure in the absence of viral load testing (CIF only group) and CIF with local targeted viral load testing (targeted VL group).

Definition of an unnecessary switch to second-line ART used three reference viral load cut-offs: <400 copies/ml; <1000 copies/ml; and the WHO recommended threshold of <5000 copies/ml.

NRTI cross-resistance was defined as the presence of ≥two TAMs, the TDF-associated mutations K65R or K70E, or the Q151M complex.

Of the 250 patients with clinical immunological failure switched to second-line ART between March 2007 and September 2009 targeted viral load testing was used in 75% (186) and 25% (64) with CIF alone. Median time on ART was 28.3 months and 25.3 months in the CIF alone and targeted VL groups, respectively.

At a viral load cut off of <1000 copies/ml 53 (21.2%) had unnecessary switches of which 30 (46.9%) were in the CIF alone group and 23 (12.4%) in the targeted VL group. At the more stringent cut-off of <400 copies/ml targeted viral load reduced unnecessary switches six-fold (46% compared to 8.6%, p<0.001). Mutations associated with cross-resistance to NRTIs in 48% of the participants comprised multiple TAMs (37%), K65R (7.1%), K70E (3.3%) or Q151M (3.3%).

One of the major strengths of the study, note the authors, is it involves a large international sample of patients diagnosed with treatment failure at a diverse range of clinics representative of current clinical practice in a number of African ART programmes.

Their study “underscores the importance of targeted viral load testing to maximise the clinical benefits of first-line regimens and prevent unnecessary switches to expensive second-line ART”. Late detection of treatment failure resulted in extensive cross-resistance to NRTIs limiting treatment options and impairing the effectiveness of [standard] second-line regimens.

The authors conclude “The development of more affordable, point of care viral load assays is a public health priority for resource-limited settings.”

Reference

Anti-HIV drug Kaletra can cause adrenal problems in newborns
By Thomas H. Maugh II, Los Angeles Times / For the Booster Shots blog
4:23 PM PDT, July 5, 2011

Using the anti-AIDS drug Kaletra prophylactically in newborn infants of HIV-positive women may cause potentially life-threatening adrenal problems in some of the infants, French researchers reported Tuesday. Although no deaths have been reported from such use, the routine prophylactic use of the drug should probably be discontinued, particularly because other effective drugs are also available, the team reported in the Journal of the American Medical Assn.

About 1% of HIV-positive women now deliver an infant who is also HIV-positive. But many HIV-negative newborns are routinely treated with HIV drugs to ensure against infection.
Kaletra, manufactured by Abbott Laboratories of Abbott Park, Ill., is a combination of the anti-AIDS drugs lopinavir and ritonavir. Lopinavir is a protease inhibitor, one of the most powerful classes of HIV drugs, and ritonavir is used to boost its efficacy. The combination is approved in the United States for treatment of children over the age of 14 days and in Europe for children over the age of 2. In March of this year, the U.S. Food and Drug Administration warned that an oral solution of the drug used to treat HIV infections in newborns could cause serious heart, kidney or breathing problems. Those problems were linked to the combination of alcohol and propylene glycol in which the drug is dissolved, and the agency warned against using it in infants younger than 14 weeks. A possible cardiac toxicity of the drug has also been reported in two sets of twins born to mothers treated with the drug.

France has a program for routine screening for congenital adrenal hyperplasia based on measuring levels of a compound called 17OHP in dried blood samples collected from newborns. Congenital adrenal hyperplasia, or CAH, is a group of inherited disorders of the adrenal glands. In girls, symptoms include abnormal menstrual periods, excessive hair, a deep voice and ambiguous genitals. In boys, symptoms include a deep voice, heavy musculature, an enlarged penis and small testicles. Both sexes have normal height as children, but are unusually short as adults. The disorder is characterized by excessive production of the hormone 17-hydroxyprogesterone (17OHP) and above-normal levels of dehydroepiandrosterone-sulfate (DHEA-S), a steroid produced primarily by the adrenal cortex.

A team headed by Dr. Albane Simon of the Hopital Necker-Enfants Malades, Assistance Publique-Hopitaux de Paris evaluated blood spots from 50 HIV-negative infants who received Kaletra after birth and compared them to spots from 108 infants who had received other drugs, including zidovudine, lamivudine and nevirapine. Among those receiving Kaletra, seven (14%) had abnormally high 17OHP levels, but none of those treated with the other drugs had abnormally high 17OHP levels. Levels of 17OHP were highest in those infants whose mothers had been treated with Kaletra during the pregnancy. The team also found unusually high levels of DHEA-S in the infants treated with Kaletra, with the highest levels again in those whose mothers had received the drug during pregnancy. All of the infants who were delivered full-term were asymptomatic, the researchers said, but three of them who were delivered prematurely experienced life-threatening conditions compatible with adrenal insufficiency, including abnormally low levels of sodium in the blood (hyponatremia), higher than normal levels of potassium (hyperkalemia, associated with kidney failure) and cardiogenic shock. All the symptoms resolved when treatment with Kaletra was stopped, but the long-term effects are unknown.

The results indicate that the drug should be used in newborns rarely, if at all, the authors said. But if it is used, the infants’ electrolytes should be carefully monitored for early signs of problems.

Museveni warns on male circumcision
Publication date: Sunday, 3rd July, 2011
By Vision Reporter
PRESIDENT Yoweri Museveni has cautioned Ugandans not to consider male circumcision as the remedy and automatic control of HIV/AIDS infection.

He said messages promoting the practice were misleading and may put the lives of many people in danger since it had not been proven to be scientifically true.

The President made the remarks during a thanksgiving service organised by the First Lady and Ruhaama MP, Janet Museveni, to thank the Lord for her landslide victory in the February polls.

The function was held at Ruhaama sub-county headquarters in Ruhaama county, Ntungamo district on Saturday.

He said if male circumcision was the answer to HIV prevention, then Ugandans who conduct circumcision as a traditional belief or a religious practice would not contract the disease.

He, however, said there is proof that these people had contracted HIV and the disease prevails in their communities.

The President emphasised abstinence from premarital sex and faithfulness in marriage as the guarantee to a life free from HIV.

During the function, Museveni highlighted the Government’s commitment to ensuring food security in homesteads and overcoming household poverty in the next five years.

Others are to develop major infrastructure and ensure excellent service delivery.
He warned government officials charged with supervision of government programmes at the grassroots and service delivery in health centres, that they risk punitive action if they are found to be negligent.

The President commended the people of Ruhaama for voting the NRM in the February elections. He particularly thanked them for overwhelmingly voting Mrs. Museveni back into Parliament. Mrs. Museveni got 86% of the votes cast, trouncing her three challengers in the race.

The President said although he was originally opposed to her joining politics, Mrs. Museveni had proved to be a great asset to the NRM and the country. He cited her contribution to development and fostering unity in her constituency and her clear ideology that looks at leadership as a sacrifice and not a source of income.

Mrs. Museveni, on her part, greatly thanked the people of Ruhaama and Ntungamo for being trustworthy and keeping their promises manifested by their voting patterns.

She commended the leaders of Ruhaama for embracing her ideology which emphasises service beyond self and selflessness in serving one's nation.

Mrs. Museveni asked leaders to emulate the example of the freedom fighters who liberated Uganda, saying they risked their lives without pay and no guarantee of safety.

She thanked the President for sparing time out of his busy schedule to attend the occasion.

Mrs. Museveni encouraged the people of Ruhaama to use these five years to give glory to God and unite in building the foundation laid in the last term.

Former Prime Minister Prof. Apollo Nsibambi said Mrs. Museveni, while state minister for Karamoja affairs, exhibited excellent management and supervisory skills that put her among the best ministers in the Government.

Nsibambi further thanked Museveni for giving him the opportunity to contribute to shaping the destiny of Uganda for the 15 years when he served the country both as minister and Prime Minister.

The main celebrant, Bishop Yona Katonene of West Ankole Diocese, said God appoints and anoints leaders at different times for different purposes.

He said leaders are worthwhile since they are God-sent.

Katonene commended the President and Mrs. Museveni for being leaders who know God and said Uganda was blessed to have them.

Katonene applauded Mrs. Museveni for her passion for the youth and children, her care for the vulnerable and her encouragement of the youth to fight HIV by abstaining from sex before marriage.

**Monkey T-Cells Don't Express Co-receptor**

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<th>SUMMARY</th>
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<td>Sooty mangabey monkeys with SIV do not experience disease progression because their CD4 T-cells express little of the CCR5 co-receptor the virus requires to enter cells.</td>
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Some species of non-human primates, including sooty mangabeys, can become infected with SIV (a simian virus closely related to HIV) but never experience disease progression including CD4 cell loss and collapsing immune function.

Researchers have studied such monkeys since the early years of the epidemic, hoping to uncover clues that might be used to help people fight HIV. Now, as reported in the June 26, 2011, issue of *Nature Medicine*, researchers have discovered that CD4 T-cells of infected mangabeys do not up-regulate expression of CCR5 co-receptors on their surface, thus blocking viral entry.

*Below is an edited excerpt from a press release issued by Emory University describing the research and its findings.***

**SIV-Resistant Monkeys Close the Gates to Viral Infection**

Sooty mangabeys, a type of African monkey, have intrigued scientists for years because they can survive infection by SIV, a relative of HIV, and not succumb to AIDS.

Researchers have identified a way some of sooty mangabeys' immune cells resist infection: they close the gates that SIV and HIV use to get into the cell. The findings may lead to strategies to help HIV-infected individuals cope better with infection.

The results are published online in the journal *Nature Medicine*.

"We have shown sooty mangabeys can prevent SIV from infecting a very important part of the immune system," says first author Mirko Paiardini, PhD, senior research scientist at Yerkes National Primate Research Center, Emory University. "This protection from infection comes from reducing the levels on the cell surface of a molecule that SIV uses to enter the cell."
Co-first author is postdoctoral fellow Barbara Cervasi. The senior author is Guido Silvestri, MD, chief of microbiology and immunology at Yerkes National Primate Research Center, Emory University. Collaborators included investigators from NIH, University of Pennsylvania, University of Pittsburgh and University Hospital Ulm.

To infect a cell, HIV and SIV need to find two molecules on the cell's surface. Scientists call these molecules co-receptors, and they can be thought of as gates. One of the co-receptors is CD4, which appears on immune cells called T cells. The other is called CCR5. Stimulating a T cell usually increases the level of CCR5, facilitating infection.

Paiardini, Cervasi and their colleagues found that in sooty mangabeys, a type of T cell called a central memory T cell doesn't turn on CCR5. This means that even when a sooty mangabey is infected with SIV, some T cells can mostly avoid being killed by the virus.

Memory T cells help the immune system respond to an infection faster and stronger the second time around. Central memory T cells are long-lived and found in lymph nodes, in contrast to effector memory T cells, which have shorter life spans and are found mostly in tissues, such as the intestines, Paiardini says.

"Not all T cells are created equal," he says. "Some appear to be more important than others for keeping the immune system up and running. This is why having central memory T cells resistant to infection is so valuable. By protecting central memory T cells, sooty mangabeys avoid the loss of T cells and the chronic immune activation that are the hallmarks of AIDS in humans."

Scientists have identified several differences in the pattern of infection between sooty mangabeys and both humans and rhesus macaques, a monkey that is susceptible to SIV infection.

"For several years, we and others thought lack of chronic immune activation was the main factor protecting sooty mangabeys from AIDS," Paiardini says. "This study changes this working model and proposes that lack of immune activation in sooty mangabey is secondary, deriving from their ability to protect and maintain their central memory T cells."

Paiardini continues, "We would have not been able to perform such complex comparative studies without the presence of the large colony of sooty mangabeys at the Yerkes National Primate Research Center."

7/5/11

Reference

Study Sheds Light on Residual Viral Load

**SUMMARY**
Residual low-level HIV plasma viremia correlates with size of the CD4 T-cell reservoir, but not immune activation markers.

**By Liz Highleyman**
Residual amounts of HIV genetic material can be detected in most people with HIV even after many years on effective combination antiretroviral therapy (ART). Viral DNA, or provirus, can remain latent inside resting CD4 T-cells, as well as anatomic areas such as the brain and gut, creating a reservoir that is impervious to current antiretroviral drugs.

But these cells can become activated in various ways, causing latent HIV to start replicating again. This is why even people with "undetectable" viral load must remain on treatment. Various strategies towards a cure for HIV aim to activate resting T-cells in order to purge or flush out the virus.

As described in the July 1, 2011, Journal of Infectious Diseases, Tae-Wook Chun and Anthony Fauci from the National Institute of Allergy and Infectious Diseases and colleagues looked at associations between residual plasma viremia, CD4 cell reservoir size, and levels of immune activation.

As previously described, Chun and Fauci's team has carried out some key studies in the area of HIV latency. In the mid-1990s they started treating a small cohort of patients whose HIV infection was diagnosed very early. Based on the half-life of latently infected CD4 T-cells and the decay of plasma HIV levels, they suggested that people who start treatment during primary infection might eliminate all virus in resting CD4 cells with 7.7 years of ART.

More recently, however, Chun and colleagues reported that while patients who started ART early had significantly less HIV DNA in their resting CD4 T-cells than those who started treatment later, all still had a small amount of residual virus, and even 1 patient with an extremely low level still experienced viral rebound after an experimental ART interruption.
In the present study the researchers assessed plasma viremia using very sensitive tests that could measure down to 0 copies/mL. They tested samples from 127 participants on ART who had undetectable plasma viral load for extended periods, as measured by standard clinical assays (limit of detection of 50 copies/mL). They used an automated system that ran the tests in quadruplicate for each individual.

**Results**

- 63% of participants with "undetectable" viral load < 50 copies/mL had detectable plasma viremia (1-49 copies/mL) according to the sensitive tests.
- 37% had no measurable plasma HIV RNA.
- The median residual viremia level was 2.7 copies/mL.
- Residual plasma HIV level correlated with the size of the CD4 T-cell viral reservoir, or cells carrying proviral DNA.
- Individuals with undetectable plasma viremia according to the sensitive tests had fewer CD4 cells carrying HIV DNA, on average, than those with detectable plasma viremia.
- Residual plasma viremia did not, however, correlate with markers of immune activation including C-reactive protein, D-dimer, interleukin 6, soluble TNF receptor I, and CD38 expression on CD4 and CD8 T-cells.

These findings, the study authors wrote, suggest that "reactivation of the latent viral reservoir may not be the sole source of residual plasma viremia."

Residual viremia "may also originate from productively infected CD4+ T-cells in various lymphoid tissues," they proposed, noting that "it is possible to have low levels of viral replication and cell-to-cell spread of virus, particularly in lymphoid organs, without such replication being reflected in the levels of plasma viremia, even as measured by the most sensitive assays."

If this is the case, they concluded, activating resting T-cells may not be enough to get rid of the virus, and "[n]ovel therapeutic strategies aimed at targeting the source of residual viremia may be necessary to achieve viral eradication."

"Achieving eradication of HIV in infected individuals receiving ART remains a daunting challenge for the scientific community," they continued in their discussion. "To achieve a functional cure, as defined by the absence of detectable HIV for extended periods of time in the absence of ART, therapeutic strategies aimed at eliminating cellular reservoirs in various tissue compartments must be accompanied by comprehensive virological assays that monitor infected CD4+ T-cells that may or may not contribute to residual plasma viremia."

**Puerto Rico Reports First Cholera Case Linked To Outbreak In Dominican Republic**

Puerto Rico has reported its first case of cholera imported by a recent traveler to the island of Hispaniola, where a cholera outbreak began in October, the Associated Press/Washington Post reports.

Health Secretary Lorenzo Gonzalez Feliciano said Monday that a 70-year-old man who had visited the Dominican Republic for a week is hospitalized in San Juan with the disease. "Health officials believe the disease is unlikely to spread because of better sanitation in the U.S. island," the news agency reports (7/4).

**Malaria-Carrying Mosquitoes Becoming Increasingly Resistant To Pyrethroid Insecticides**

Mosquitoes that carry malaria are increasingly becoming resistant to pyrethroid insecticides, which are the only insecticides approved by the WHO to treat bed nets and are the most effective and cost efficient for indoor spraying, Nature News reports.

By the end of the year, the WHO plans "to launch a global strategy to tackle the problem," including recommending "that control programs rotate insecticides sprayed indoors, using pyrethroids one year and a different class the next. This would be more costly and less effective than relying only on pyrethroids, however, so control programs may be reluctant to adopt this measure," the news service writes. In the long term, new insecticides will be needed to combat the disease, according to researchers (Butler, 7/5).

**Reference**

UPDATE: Federal Appeals Court Overturns United States "Prostitution Pledge" for U.S. Groups; Int'l Orgs Still Subject to Pledge
by Jodi Jacobson, Editor-in-Chief, RH Reality Check
July 6, 2011 – 3:21pm (Print)

UPDATE: This article was amended at 8:00 pm, Wednesday, July 6th, 2011 to confirm that today's decision applies only to the organizations named in the suit and does not apply to international and country-level organizations established outside the U.S.

Correction: This article was amended at 4:08 pm on Wednesday, July 6th, 2011 to reflect the fact that the implications of the court decisions for non-U.S. organizations is not yet clear.

A federal appeals court today ruled that the United States cannot force organizations receiving U.S. funding to "denounce" prostitution and sex trafficking as a condition for applying for or using U.S. international HIV and AIDS funding. The suit was originally filed by two U.S. groups, the Alliance for Open Society International and Pathfinder International in 2005; two other organizations, the Global Health Council and InterAction, joined the suit in 2008.

The court found that the "prostitution pledge" or "anti-prostitution loyalty oath," as it came to be known, was not constitutional because it compels organizations to adopt and espouse a government viewpoint, and that "[c]ompelling speech as a condition of receiving a government benefit cannot be squared with the First Amendment." The majority opinion condemned the requirement as "viewpoint-based, because it requires recipients to take the government's side on a particular issue. It is well established that viewpoint-based intrusions on free speech offend the First Amendment."

The pledge was originally inserted by New Jersey Republican Congressman Chris Smith as an amendment to the 2003 U.S. Global Leadership Act Against AIDS, Tuberculosis and Malaria, the legal basis of the President's Emergency Plan for AIDS Relief (PEPFAR). As ultimately interpreted by the Bush Administration (including the Global AIDS Coordinator in the Department of State and the Department of Justice under Bush) the pledge required organizations to promise not to "promote or support prostitution" while implementing U.S.-funded programs to fight the spread of HIV and attempting to end the AIDS epidemic.

The Obama Administration, to the dismay of public health and human rights advocates, has kept the pledge in force.

The pledge, which as defined by the Bush Administration applied to speech and activities funded not only by the U.S. government but by other private sources of funding, was and has continued to be criticized by the global public health and human rights communities for a number of reasons. Among other problems, the language of the pledge is incredibly vague and does not effectively define what constitutes "promoting" prostitution. For example, is helping sex workers find health care "promoting prostitution?" Is ensuring that sex workers have access to condoms "promoting prostitution?" Does providing vulnerable street-based sex workers with a place to sleep and use a toilet constitute "promoting prostitution?" From the beginning, the inability to answer these and other questions created a chilling effect on organizations doing work to prevent HIV infections because, in fear of violating a policy they could not define and thereby losing their funding, programs that might otherwise been funded were dropped, irrespective of whether the strategies involved had been proven to reduce the spread of HIV.

Moreover, programs recognized around the world for their successes in working with marginalized populations such as sex workers and other marginalized populations have been de-funded. The pledge also required health workers to become quasi-law enforcement agents, undoing years of work building trust among vulnerable populations such as street- and brothel-based sex workers in countries like Cambodia, India, Thailand, and Vietnam. Finally, it prevented U.S. organizations receiving either U.S. or private funds from supporting the efforts of sex worker collectives to promote universal condom use, safe sex practices, to defend themselves against police violence and corruption, or to fight to secure their basic human rights.

According to the Associated Press, the 2-to-1 ruling by the U.S. 2nd Circuit Court of Appeals in New York upheld a lower court decision.

"Today's victory has profound implications not only for the rights of private, non-governmental organizations to operate without undue government interference, but for the health of vulnerable women, men, and adolescents in less developed countries," Pathfinder President Daniel E. Pellegrom, said.

"Any organization that works to address the tragedy of HIV and AIDS must confront head on the need to serve sex workers, but the loyalty oath undermines our efforts by forcing us to stigmatize the very people we are trying to reach."
Still the ruling, while a critical step forward, is nonetheless a partial victory for women's rights because it applies only to U.S. non-profit groups and does not lift the pledge requirements from international (non-US) or local NGOs in other countries doing critical HIV and human rights work. To make true progress on HIV and AIDS, and on the rights of all persons engaged in sex work, human rights and health advocates argue that the pledge must be removed as a condition of aid to any and all groups.

**Study reveals why some men fear circumcision**

Published on 06/07/2011
By Nicholas Anyuor

The length of post-surgical period one is required to abstain from sex is among reasons discouraging men from going for circumcision in Nyanza.

A study indicates some men believed they would have to abstain from sex for up to six months, which many consider too long a period.

The World Health Organisation and the joint United Nations Programme on HIV and Aids recommend abstaining from sex for six weeks, for the wound to heal completely.

The studies were conducted by researchers from the University of Illinois at Chicago (UIC), the Nyanza Reproductive Health Society (NRHS), Impact Research and Development Organisation and the University of Nairobi with support from the Male Circumcision Consortium in three districts in the province.

The study participants also cited missing time from work during the healing period after the procedure as one of the deterrents.

The men believed that one could be away from work from one to 12 weeks as the wound healed.

"The recommended time is actually about four days for those who are engaged in physical labour, while those who do sedentary jobs can resume work immediately after the procedure," explained Dr Walter Obiero, the clinical manager at the Nyanza Reproductive Health Society.

The study, carried out in the month of May, involved 121 men, of ages 18 to 40. The subjects were recruited at market places, shopping centres, and workplaces in Kisumu East, Nyando and Kisumu West districts in Kisumu County.

**The study group**
The study targeted bicycle transporters and other workers in the informal sector, students, farmers, business people, teachers, fishermen, drivers, and religious leaders.

The study also revealed that fear of complications, such as bleeding, pain, and delayed healing, was also a hindrance to the exercise.

"Men think these side effects are much more common than they actually are. Just 2.7 per cent of circumcised men in Kenya reported complications after the surgery, all of which were resolved with treatment," said Obiero.

However, HIV/Aids prevention was not the most common reason mentioned for choosing male circumcision, according to the study.

Some participants were hesitant to believe that the procedure offers partial protection against HIV infection because they did not understand how it could be protective.

"We have to do continuous advocacy, coupled with correct messaging about male circumcision, to win over those shying away due to misconceptions," said Dr Charles Okal, the provincial Aids and STI coordinator in Nyanza.

**Unexpected cell repairs the injured spinal cord**

Lesions to the brain or spinal cord rarely heal fully, which leads to permanent functional impairment. After injury to the central nervous system (CNS), neurons are lost and largely replaced by a scar often referred to as the glial scar based on its abundance of supporting glial cells. Although this process has been known to science for over a century, the function of the scar tissue has long been disputed. However, there are indications that it stabilizes the tissue and that it inhibits the re-growth of damaged nerve fibres.

In this present study, Professor Jonas Frisén and his team of researchers show that the majority of scar cells in the damaged spinal cord are not glial cells at all, but derive from pericytes, a small group of cells located along blood vessels. They reveal that these pericytes start to divide after an injury, giving rise to a mass of connective tissue cells that migrate towards the lesion to form a large portion of the scar tissue. Their paper also shows that these cells are needed to regain the tissue integrity, and that in the absence of this reaction, holes appear in the tissue instead of scarring.
For many years, scientists have tried to modulate scar formation after CNS damage in order to facilitate functional recovery, and have concentrated on glial cells. However, these new findings indicate a critical and previously unknown mechanism for scar formation following damage to the nerve system, and give reason for further investigation into whether the modulation of pericytes after CNS injury can stimulate functional recovery.

**Publication:** "A pericyte origin of spinal cord scar tissue", C. Göritz, D. Dias, N. Tomilin, M. Barbacid, O. Shupliakov, J. Frisén, Science online 7 July 2011.

**Journal website:** [http://www.sciencemag.org/](http://www.sciencemag.org/)

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**Discovery of natural antibody brings a universal flu vaccine a step closer**

An academic-industry collaboration by Scripps Research and Crucell finds broadly acting antibody against influenza viruses

LA JOLLA, CA – July 7, 2011 – Annually changing flu vaccines with their hit-and-miss effectiveness may soon give way to a single, near-universal flu vaccine, according to a new report from scientists at The Scripps Research Institute and the Dutch biopharmaceutical company Crucell. They describe an antibody that, in animal tests, can prevent or cure infections with a broad variety of influenza viruses, including seasonal and potentially pandemic strains.

The finding, published in the journal *Science* Express on July 7, 2011, shows the influenza subtypes neutralized with the new antibody include H3N2, strains of which killed an estimated one million people in Asia in the late 1960s.

"Together this antibody and the one we reported in 2009 have the potential to protect people against most influenza viruses," said Ian Wilson, who is the Hansen Professor of Structural Biology and a member of the Skaggs Institute for Chemical Biology at Scripps Research, as well as senior author of the new paper with Crucell's chief scientific officer Jaap Goudsmit.

**Tackling a Major Shortcoming**

Wilson’s laboratory has been working with Crucell scientists since 2008 to help them overcome the major shortcoming of current influenza vaccines: They work only against the narrow set of flu strains that the vaccine makers predict will dominate in a given year, so their effectiveness is temporary. In addition, current influenza vaccines provide little or no protection against unforeseen strains.

These shortcomings reflect a basic flu-virus defense mechanism. The viruses come packaged in spherical or filamentous envelopes that are studded with mushroom-shaped hemagglutinin (HA) proteins, whose more accessible outer structures effectively serve as decoys for a normal antibody response. "The outer loops on the HA head seem to draw most of the antibodies, but in a given strain these loops can mutate to evade an antibody response within months," said Wilson. Antiviral drugs aimed at these and other viral targets also lose effectiveness as flu virus populations evolve.

"The major goal of this research has been to find and attack relatively unvarying and functionally important structures on flu viruses," said Damian Ekiert, a graduate student in the Scripps Research Kellogg School of Science and Technology who is working in the Wilson laboratory. Ekiert and Crucell’s Vice President for Antibody Discovery Robert H. E. Friesen are co-first authors of the Science Express report.

By sifting through the blood of people who had been immunized with flu vaccines, Goudsmit and his colleagues several years ago discovered an antibody that bound to one such vulnerable structure. In mice, an injection of the antibody, CR6261, could prevent or cure an otherwise-lethal infection by about half of flu viruses, including H1 viruses such as H1N1, strains of which caused deadly global pandemics in 1918 and 2009.

The Crucell researchers approached Wilson, whose structural biology lab has world-class expertise at characterizing antibodies and their viral targets. Ekiert, Wilson, and their colleagues soon determined the three-dimensional molecular structure of CR6261 and its binding site on HA, as they reported in Science in 2009. That binding site, or "epitope," turned out to be on HA's lower, less-accessible stalk portion. The binding of CR6261 to that region apparently interferes with flu viruses' ability to deliver their genetic material into host cells and start a new infection. That antibody is about to begin tests in human volunteers.

**The Missing Piece**

Cruell researchers subsequently searched for an antibody that could neutralize some or all of the remaining flu viruses unaffected by CR6261, and recently found one, CR8020, that fits this description. As the team now reports in the Science Express paper, CR8020 powerfully neutralizes a range of human-affecting flu viruses in lab-dish tests and in mice. The affected viruses include H3 and H7, two subtypes of
great concern for human health that have already caused a pandemic (H3) or sporadic human infections (H7).

As with the CR6261 project, Ekiert and colleagues were able to grow crystals of the new antibody bound to an HA protein from a deadly strain of H3N2, and to use X-ray crystallography techniques to determine the antibody's structure and its precise epitope on the viral HA protein.

"It's even lower on the HA stalk than the CR6261 epitope; in fact it's closer to the viral envelope than any other influenza antibody epitope we've ever seen," said Ekiert.

Crucell is about to begin initial clinical trials of CR6261 in human volunteers, and the company expects eventually to begin similar trials of CR8020. If those trials succeed, aside from a vaccine the two antibodies could be combined and used in a "passive immunotherapy" approach. "This would mainly be useful as a fast-acting therapy against epidemic or pandemic influenza viruses," said Wilson. "The ultimate goal is an active vaccine that elicits a robust, long-term antibody response against those vulnerable epitopes; but developing that is going to be a challenging task."

"A Highly Conserved Neutralizing Epitope on Group 2 Influenza A Viruses,"

Drug Designer
New tool reveals mutations that cause HIV-drug resistance
July 8, 2011
Protease inhibitor drugs are one of the major weapons in the fight against HIV, the virus that causes AIDS, but their effectiveness is limited as the virus mutates and develops resistance to the drugs over time. Now a new tool has been developed to help predict the location of the mutations that lead to drug resistance.

First discovered in 1995, protease inhibitor drugs have dramatically reduced the number of AIDS deaths. Taken in combination with two other anti-HIV drugs, protease inhibitors work by halting the action of the protease enzyme, a protein produced by HIV that is necessary for replication of the virus. However, almost half of HIV patients who initially respond to treatment with protease inhibitors develop drug-resistance strains and stop responding to treatment within eight to 10 months.

Currently there are nine FDA approved protease inhibitors, and 21 most common drug-resistant mutations.

The main reason for the short-term effectiveness of the drug has to do with the evolution of the drug within the body, said the study's author, Yi Mao, a postdoctoral fellow at the National Institute for Mathematical and Biological Synthesis.

In the new study, published in the journal BMC Structural Biology, Mao used a mathematical modeling technique called elastic network modeling to examine the physical properties and interactions of the proteins. The model reveals where mutations are occurring during the evolution of the HIV-virus proteins and how these mutations help the virus survive. "With this kind of knowledge, better strategies for designing anti-HIV drugs could be developed," Mao said.

HIV kills the body's immune system cells, called CD4 cells. Once the number of CD4 cells dips below 200, an HIV patient enters the last stage of his or her disease: Acquired Immune Deficiency Syndrome, or AIDS. The first cases of AIDS were reported thirty years ago. Since then, more than 60 million people have been infected with HIV, and more than 30 million people have died from AIDS. Today an estimated 34 million people worldwide are living with HIV – 1.2 million in the U.S.

Citation: Mao Y. 2011. Dynamical Basis for Drug Resistance of HIV-1 Protease. BMC Structural Biology.
Published [online] 8 July 2011.

Hepatitis A Vaccine Response Durable in People with HIV

By Liz Highleyman
Hepatitis A virus (HAV) can cause more aggressive liver disease in people with HIV, and experts recommend that individuals who are diagnosed as HIV positive should be vaccinated against hepatitis A and B (there currently is no effective hepatitis C vaccine).

As described in the June 2011 Journal of Infectious Diseases, Nancy Crum-Cianflone and fellow investigators with the Infectious Disease Clinical Research Program HIV Working Group looked at durability of HAV vaccine protection in the HIV positive population.
This retrospective analysis included 130 HIV positive adults in the U.S. Military HIV Natural History Study; most were men and the median age was 35 years. The median CD4 cell was quite high, at 461 cells/mm³ (near the threshold for starting antiretroviral treatment according to current U.S. guidelines), and about half had HIV RNA viral load < 1000 copies/mL; 62% were taking antiretroviral therapy (ART).

All participants received the standard 2 doses of HAV vaccine. The researchers analyzed blood specimens collected at 1 year, 3 years, and, if available, 6 to 10 years after vaccination. HAV immunoglobulin G (IgG) antibody levels of 10 mIU/mL or greater were considered protective.

Results

- 89% of HIV positive participants achieved initial vaccine responses, compared with 100% of HIV negative historical controls (that is, results seen in prior studies).
- Among HIV positive initial responders with available follow-up specimens, longer-term response rates remained high:
  - 89% protection at 1 year;
  - 90% still HAV antibody positive after 3 years;
  - 85% still protected after 6 to 10 years.
- However, average HAV antibody concentrations were lower in HIV positive people compared with HIV negative controls:
  - 1 year: 154 vs 1734 mIU/mL, respectively;
  - 3 years: 111 vs 687 mIU/mL, respectively;
  - 6-10 years: 64 vs 684 mIU/mL, respectively;
- People with CD4 cell counts > 350 cells/mm³ when vaccinated were more likely to achieve an initial response than those with lower levels (94% vs 78%, respectively), but this was no longer statistically significant at 3 years.
- Over time, among HIV participants, higher HAV antibody levels were significantly associated with low HIV viral load.

Based on these findings, the investigators concluded, "Most adults with well-controlled HIV infections had durable seropositive responses up to 6-10 years after HAV vaccination."

"Maintaining suppressed HIV RNA levels among HIV-infected persons may be an important strategy for sustaining durable antibody levels for vaccine preventable infections such as hepatitis A virus," they suggested. 7/8/11

Reference

**Can Alcohol Abuse Drug Disulfiram Help Eradicate HIV?**

**SUMMARY**
Disulfiram (Antabuse), a medication prescribed to manage alcoholism, can activate resting CD4 cells and flush out latent HIV, a key step towards viral eradication.

**By Liz Highleyman**
Researchers are increasingly exploring a variety of strategies towards a cure for HIV. But eradicating the virus has proven difficult, in part because HIV integrates its genetic material, known as proviral DNA, into human cells.

HIV DNA can remain latent in resting CD4 T-cells for years or decades, where it is safe from current antiretroviral drugs. Eventually, however, these reservoir cells can become activated and start releasing new virus, which is why people with HIV must remain on antiretroviral therapy indefinitely even when their plasma viral load is undetectable.

One strategy for eradicating HIV from the body—or reducing it to a low enough level that the immune system can control it—involves forcibly activating resting CD4 cells carrying proviral DNA, in order to flush out the viral reservoir and render the virus susceptible to antiretroviral therapy (ART).
Many compounds can activate resting CD4 cells, but some do so too well: stimulating too many T-cells can lead to life-threatening excessive immune activation known as a cytokine storm. Researchers are therefore looking for more selective activating agents.

Sifei Xing, Robert Siliciano, and colleagues at Johns Hopkins School of Medicine developed a new system for screening large numbers of compounds in a laboratory model of CD4 cells, seeking those that can flush out HIV without toxic side effects. They have tested both novel compounds and existing drugs approved for a variety of indications, mostly cancer chemotherapies.

As described in the June 2011 Journal of Virology, the researchers reported that one widely used compound, disulfiram, appears to reactivate latent HIV without global T-cell activation. Disulfiram is FDA-approved for managing alcohol abuse, as it causes unpleasant symptoms including flushing, nausea, and headache when alcohol is consumed.

These findings led the researchers to conclude, "The extent to which disulfiram reactivates latent HIV-1 in patient cells is unclear, but the drug alone or in combination may be useful in future eradication strategies."

Steven Deeks at the University of California San Francisco and colleagues are conducting a pilot study to evaluate how well disulfiram activates resting CD4 cells and flushes out HIV in patients. Further details about the trial—which is ongoing but no longer recruiting participants—are available at http://clinicaltrials.gov/ct2/show/NCT01286259, 7/8/11

Reference

Older HIV Drugs Contribute to Accelerated Aging

HIV patients treated with early NRTI drugs show evidence of mitochondrial DNA damage similar to that usually seen in much older people.

As people with HIV live longer due to effective antiretroviral therapy (ART), aging has become a key concern. A growing body of evidence suggests that HIV positive people may experience faster than normal aging, characterized by premature progressive organ disease and frailty.

Early nucleoside reverse transcriptase inhibitors (NRTIs) such as zidovudine (AZT; Retrovir), didanosine (ddI; Videx), and stavudine (d4T; Zerit) have been linked to mitochondrial toxicity, or damage to energy-producing structures within cells. While these drugs are no longer recommended in the U.S. and Europe, they are inexpensive and therefore still commonly used in resource-limited countries.

Study results reported recently in the advance online edition of Nature Genetics suggest that this mitochondrial DNA damage plays a role in accelerated aging. Below is an edited excerpt from a press release issued by the Wellcome Trust in the UK describing the findings.

Premature Aging Caused By Some HIV Drugs, Study Shows

June 26, 2011—A class of anti-retroviral drugs commonly used to treat HIV, particularly in Africa and low income countries, can cause premature ageing, according to research published today in the journal Nature Genetics. The study shows that the drugs damage DNA in the patient's mitochondria—the "batteries" which power their cells.

The findings may explain why HIV-infected people treated with antiretroviral drugs sometimes show advanced signs of frailty and age-associated diseases such as cardiovascular disease and dementia at an early age.

Nucleoside analogue reverse-transcriptase inhibitors (NRTIs)—of which the most well known is zidovudine, also known as AZT—were the first class of drug developed to treat HIV. They were a major breakthrough in the treatment of the disease, greatly extending lifespan and leading the condition to be seen as a chronic, rather than terminal, condition.

In high-income countries, such as Europe and North America, the older NRTIs are used less commonly now due to concerns over toxicity and side effects when taken over a long period of time. However, as they are now off-license and hence relatively cheap, the drugs have proved to be an important lifeline for people infected with HIV in Africa and low income countries.

Professor Patrick Chinnery, a Wellcome Senior Fellow in Clinical Science from the Institute of Genetic Medicine at Newcastle University, says: "HIV clinics were seeing patients who had otherwise been successfully treated but who showed signs of being much older than their years. This was a real mystery. But colleagues recognized many similarities with patients affected by mitochondrial diseases—conditions that affect energy production in our cells—and referred them to our clinic."
Mitochondria are the "batteries" in our cells which provide them with the energy to carry out their functions. During natural human ageing, these mitochondria acquire mutations, though it is unclear whether these mutations are a cause of ageing or a consequence.

In an attempt to understand what was happening at a cellular level, Professor Chinnery and colleagues studied muscle cells from HIV-infected adults, some of whom had previously been given NRTIs.

The researchers found that patients who had been treated with NRTIs—even as long ago as a decade previously—had damaged mitochondria which resembled that of a healthy aged person. "The DNA in our mitochondria gets copied throughout our lifetimes and, as we age, naturally accumulates errors," explains Professor Chinnery. "We believe that these HIV drugs accelerate the rate at which these errors build up. So over the space of, say, ten years, a person's mitochondrial DNA may have accumulated the same amount of errors as a person who has naturally aged twenty or thirty years. What is surprising, though, is that patients who came off the medication many years ago may still be vulnerable to these changes."

Co-author and HIV specialist, Dr Brendan Payne, a Medical Research Council fellow from the Department of Infection and Tropical Medicine at the Royal Victoria Infirmary, Newcastle, believes that despite the side effects caused by NRTIs, they are still important drugs and the risks are relative. "These drugs may not be perfect, but we must remember that when they were introduced they gave people an extra ten or twenty years when they would otherwise have died," he says. "In Africa, where the HIV epidemic has hit hardest and where more expensive medications are not an option, they are an absolute necessity."

Professor Chinnery and colleagues are now looking at ways to repair or stall some of the damage caused by the medication and believe that focusing on exercise—which appears to have a beneficial effect on patients with mitochondrial diseases—may help.

The study was funded by the Medical Research Council, the British Infection Society, the Newcastle Healthcare Charity, the UK NIHR Biomedical Research Centre for Aging and Age-related Disease and the Wellcome Trust. 7/8/11

Reference

**Damage to Blood-Brain Barrier May Explain Neurocognitive Problems**

**SUMMARY**
HIV weakens the blood-brain barrier, which may help explain low-level cognitive impairment in people with HIV despite effective antiretroviral treatment.

**By Matt Sharp**
Numerous studies have shown that people with HIV are more likely to experience mild-to-moderate cognitive impairment, and at an earlier age, than HIV negative people. The precise reason for this is not well understood. HIV enters the brain during early infection, but does not infect neurons.

Eliseo Eugenin from Albert Einstein College of Medicine in New York City and his colleagues have been studying astrocytes for years. These cells are an integral part of the blood-brain barrier, a network of blood vessels that protects the brain from toxins and other harmful substances. Astrocytes help to support the blood vessels that make up the barrier wall.

As described in the June 29, 2011, Journal of Neuroscience, using human cells in a laboratory model the team found that HIV infects approximately 5% of astrocytes. They saw similar results in a previous study in 2007. Infection of even this small proportion of astrocytes led to the death of others nearby, making the blood-brain barrier more porous.

The researchers next looked at structures called gap junctions that telegraph chemical signals from one astrocyte to others. They found that the HIV-infected astrocytes emit toxic signals that kill other surrounding uninfected astrocytes, compromising the integrity of the blood brain barrier. Blocking gap junctions prevented changes to the barrier, indicating that these lethal signals are transmitted via these junctions.

"This [blood-brain barrier] disruption is due to endothelial apoptosis, misguided astrocyte end feet, and dysregulation of lipoxygenase/cyclooxygenase, BKCa channels, and ATP receptor activation within astrocytes," the study authors wrote. "All of these alterations in [blood-brain barrier] integrity induced by a few HIV-infected astrocytes were gap junction dependent, as blocking these channels protected the [blood-brain barrier] from HIV-infected astrocyte-mediated compromise."
Eugenin's team performed similar experiments using brain tissue from macaque monkeys infected with simian immunodeficiency virus (a relative of HIV), and found that infected astrocytes had the same effect on surrounding cells.

"Researchers have been stymied to explain why HIV-associated neurological complications persist, despite potent combination antiviral therapies that have dramatically improved health and survival," said Igor Grant from the University of California at San Diego in a press release issued by the Society for Neuroscience, which publishes the journal. "This study provides a possible explanation indicating that minute numbers of infected astrocytes can trigger a cascade of signals that could open the brain to various toxic influences."

While antiretroviral therapy has been useful in preventing serious neurological problems such as severe dementia and meningitis, 40% to 60% of people with HIV still have low-level cognitive impairment. As people with HIV age and are at higher risk for neurocognitive decline, this research may lead to new treatment approaches to block or modify these signaling pathways that lead to cell death and weakening of the brain's protective barrier.

Reference

Viruses Bathe in Rivers and at the Beach, Too, European Study Finds
ScienceDaily (July 9, 2011) — European researchers have found viruses in nearly 40% of more than 1,400 bathing water samples gathered from coastal and inland areas in nine countries, including Spain. The concentrations found are low, but the scientists are calling for these microorganisms to be monitored in recreational waters, above all at times when their populations skyrocket, as is the case after heavy rains.

The European Bathing Water Directive establishes maximum levels for bacteria, in particular Escherichia coli and intestinal enterococcus, which must not be exceeded in order to maintain water quality. For viruses, however, the regulation only suggests that scientific studies should be carried out to help determine reference parameters and reliable detection methods.

Against this backdrop, 16 research groups from the Virobathe project, which is financed by EU funds, analysed the presence of adenoviruses (viruses with DNA) and noroviruses (which have RNA and cause gastroenteritis) in 1,410 samples of swimming water, both freshwater and seawater, in nine European countries. In Spain, for example, scientists from the University of Barcelona (UB) focused on the beaches at Gavà.

The overall results showed that 553 samples contained viruses (39.2% of the total), above all adenoviruses (in 36.4% of the samples, compared with just 9.4% for noroviruses), and more were found in freshwater than saltwater. A small selection of samples also showed that a quarter of the microorganisms had infectious capacity.

Adenoviruses are associated with gastroenteritis in children, some respiratory infections, ear infections and conjunctivitis, although a large part of the population has already been in contact with them and so is resistant to infection by most of the strains.

The study, which has been published in the journal Water Research, says that the presence of infectious adenoviruses and noroviruses in water samples "could pose a risk to health."

More microorganisms after storms
"In general, adenoviruses do not necessarily pose a significant risk to the population (if they are common strains that have already infected most people in childhood and if they remain at low levels). However, we know that virus numbers in bathing waters increase following heavy rains, meaning they could end up reaching dangerous levels," says Rosina Girones, director of the UB’s Laboratory of Water and Food Viral Pollution and co-author of the study.

Viruses take longer than bacteria—which are used as standard indicators—to return to acceptable levels following heavy rains. In addition, many virus communities survive waste water treatment processes better than bacteria, and are more resistant to seawater.

The researcher highlights the importance of this study: "It shows that we already have a reliable technique that can be easily standardised (quantitative PCR) for detecting and quantifying viruses in bathing waters, which makes it possible to estimate the faecal contamination and quality of water. Aside from this there is no clear correlation between the levels of bacterial indicators cited in the regulation and the presence of the viruses studied."
The data obtained also lend support to the idea of using measurements of human adenoviruses, which are excreted all year long in every geographical area, and are found in 100% of waste water samples, as an indicator of viral water contamination. The Catalan laboratory is one of the promoters of this initiative in Europe.

The Spanish group is currently also participating in the international Viroclime project with four other EU countries and Brazil, in order to analyse the impact of climate change on the dispersal of pathogenic viruses in rivers, lakes and at beaches.

Journal References:

2. Silvia Bofill-Mas, Byron Calgua, Pilar Clemente-Casares, Giuseppina La Rosa, Marcello Iaconelli, Michele Muscillo, Saskia Rutjes, Ana Maria Roda Husman, Andreas Grunert, Ingeburg Gräber, Marco Verani, Annalaura Carducci, Miquel Calvo, Peter Wyn-Jones, Rosina Girones. Quantification of Human Adenoviruses in European Recreational Waters. Food and Environmental Virology, 2010; 2 (2): 101 DOI: 10.1007/s12265-010-9035-4

Pre-existing immune deficiency main cause of AIDS-defining cancers in patients starting HIV therapy

Michael Carter
Published: 11 July 2011

New research has underlined the importance of the timely initiation of antiretroviral therapy. In a paper published in the online edition of AIDS, investigators from the European CASCADE collaboration showed that the risk of AIDS-defining cancers in patients starting HIV therapy was associated with severe immune deficiency in the preceding year.

“An initially low and decreasing CD4 cell count during the year prior to cancer diagnosis is predictive of both Kaposi sarcoma and NHL [non-Hodgkin lymphoma],” comment the authors.

However, their results also showed that the incidence of both these cancers was increased in the three months following the initiation of antiretroviral therapy.

The investigators emphasise, “most of this increased cancer risk is explained by the immunodeficiency characteristic of the period before cART [combination antiretroviral therapy] initiation.”

But they add, “there may be some additional risk resulting from immune reconstitution during the first few months after cART initiation.”

Immune reconstitution inflammatory syndrome (IRIS) in patients with HIV involves a worsening of health soon after antiretroviral therapy is started. It can involve either a deterioration of an existing condition, or the “unmasking” of sub-clinical disease.

Most of the research into antiretroviral-related IRIS has focused on opportunistic infections such as tuberculosis (TB). However, studies have also identified Kaposi’s sarcoma IRIS.

Investigators from the Concerted Action on SeroConversion to AIDS and Death in Europe (CASCADE) collaboration wanted to establish a clearer understanding of the risks associated with the development of the AIDS-defining cancers Kaposi’s sarcoma and non-Hodgkin’s lymphoma in the period after the initiation of HIV therapy. The investigators especially wanted to see if the risk of these cancers was associated with immune deficiency in the period before treatment was started, or if any of the risk to be attributed to IRIS.

They therefore designed a case-controlled study. Cases were patients who developed a cancer, and each case patient was matched with up to ten controls.

All the cases had a minimum of two CD4 cell count measurements in the year before their cancer diagnosis. The cases also had similar CD4 data for a reference year.

A total of 689 cases were eligible for inclusion in the study, and they were matched with 4588 controls.

During the year before diagnosis (or the reference year), 31% of cases but only 6% of controls had a CD4 cell count below 100 cells/mm³.

In the year before the diagnosis of Kaposi’s sarcoma or non-Hodgkin’s lymphoma (or the reference year), CD4 cell counts in the case patients fell by an average of 16% compared to a fall of just 2% in the controls.
Analysis showed that patients with a low or falling CD4 in the year preceding had an increased risk of developing an AIDS-defining cancer. The risk of these malignancies increased as patients’ immune function deteriorated. The association between a poorer and deteriorating immune system was significant even when analysis was restricted to the period after 2000.

However, the investigators also found some evidence that the risk of cancer was increased in the period shortly after HIV therapy was started.

They explain, “there was a significant trend toward an increasing [risk] of cancer as the interval between cART initiation and the reference date decreased.”

An increased risk of an AIDS-defining cancer was seen in patients who started HIV therapy within the previous three months (OR = 2.31; 95% CI, 1.33-4.00).

“Given the known associations of Kaposi sarcoma and NHL with underlying viral infections...it would not be surprising to observe these cancers occurring or worsening in the context of IRIS,” write the authors.

However, they add, “most of the excess cancer risk in patients initiating cART reflects the immunodeficiency that most likely led to the use of cART.”

The authors conclude, “the main risk factor for the appearance of these malignancies is immunodeficiency; and, therefore, the timely initiation of cART remains the best strategy to avoid the development of these malignancies.

Reference

Gay men hit hard by HIV/AIDS
Updated: 2011-07-11 07:55
By Shan Juan (China Daily)
BEIJING—Gay and bisexual men account for around one in every three new cases of HIV in China, according to the latest official statistics released by the Ministry of Health.

About 5 percent of the group—officially termed men who have sex with men, or MSM—are living with the virus, which is a rate that is 88 times higher than the national HIV prevalence rate of 0.057 percent.

The problem is particularly acute in large urban centers, with the prevalence rate in some southwestern cities reaching almost 20 percent.

However, the statistics also show that less than half of all gay and bisexual men have access to HIV screening, while about 15 percent of those who are infected are not receiving treatment.

“Cities are at the heart of China’s development and progress and must remain at the forefront of its HIV response,” said Michel Sidibe, executive director of the Joint United Nations Programme on HIV/AIDS (UNAIDS), during a workshop about the HIV impact on MSM on Saturday in Chengdu, capital of Southwest China's Sichuan province.

"Through bold action cities can lead the way to achieving the UNAIDS vision of zero new HIV infections, zero discrimination and zero AIDS-related deaths," he said, according to a UNAIDS news release. "We hope that over the next year, many more Chinese cities will implement MSM strategies."

Almost 10 percent of gay and bisexual men in Chengdu are HIV-positive, according to Yang Xiaoguang, director of the city’s health bureau. He agreed with Sidibe that cities have a crucial role to play in AIDS prevention and added: "By working to build a strong, multi-sector response in Chengdu, with meaningful community participation, we can scale-up coverage of prevention, treatment and care services among MSM and halt the spread of HIV."

During the workshop, senior Chinese health officials, representatives from civil societies and other delegates discussed a new five-year strategy that increases coverage of HIV prevention and treatment for the MSM population and promotes the participation of community organizations.

Government estimates put China’s population of gay men at between 5 and 10 million, although Zhang Beichuan, a leading expert on HIV at Qingdao University, puts the number closer to 30 million.

Tong Ge, coordinator of China’s MSM Health Forum, noted the importance of ensuring strong cooperation between the government and society.

"By building on the experiences of cities like Chengdu, which already have well developed AIDS responses, we can help promote multi-sector collaboration on an equal, orderly basis and strengthen the response to HIV nationwide,” he said. "The next step will be to implement similar strategies in other cities nationwide."

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Chengdu’s new strategy underscores the critical role community organizations can play in reaching MSM and other populations at a higher risk of infection, experts at the workshop said. In 2009, China had an estimated 740,000 people living with HIV/AIDS, according to UNAIDS statistics.

**HIV Entrenched in South’s Poorest Counties**

*USA Today*, (07.11.2011) Steve Sternberg; Jack Gillum

Though HIV is still viewed by some as a gay and urban problem, a new county-level map of infection data shows the vast inroads AIDS has made in America’s heartland, particularly the South.

County data presented in map form by researchers at Emory University’s Rollins School of Public Health, along with an analysis by USA Today, find the Southern counties with the greatest HIV infection rates are some of the nation’s poorest. On average, one in seven people in US counties with the highest infection rates live in poverty. In the South, that figure jumps to one in five.

Dr. Jonathan Mermin, director of HIV/AIDS prevention at CDC, confirms the link between HIV and poverty. “People with household incomes of less than $10,000 a year were 10 times more likely to have HIV than people whose household incomes are greater than $50,000,” he said.

Rolling Fork, Miss., is typical. The tiny farming community’s HIV infection rate, 249 cases for every 100,000 people, is comparable to that of New York or San Francisco. Roughly 35 percent of county residents live under the federal poverty limit. Unemployment in Rolling Fork stands at about 10 percent. Most residents are black.

Rolling Fork Mayor James Denson said he was unaware that the community’s HIV rate is so high. But Michael Baker, one of three doctors in the community, was not surprised. “That may just be the tip of the iceberg, unfortunately,” Baker said.

Jackson, Miss., AIDS activist Cedric Sturdevant said homophobia plays a key role. “You don’t want people to know you’re homosexual, if that’s the case. If you’re heterosexual and you get infected, you don’t want people to put you in the category of being homosexual,” he noted. “People don’t want to get into care because they’re afraid their families will find out” and reject them.

**Scientists Find First Superbug Strain of Gonorrhea**

*Reuters*, (07.11.2011) Kate Kelland

The first report of a strain of gonorrhea highly resistant to all cephalosporin-class antibiotics is being presented today at the 19th Biennial Conference of the International Society for Sexually Transmitted Disease Research in Quebec. The new strain, dubbed H041, was found in Kyoto, Japan, and cannot be killed by any currently recommended treatments. New and untested drugs may have to be applied in treating such “superbug” gonorrhea, experts said.

“Since antibiotics became the standard treatment for gonorrhea in the 1940s, this bacterium has shown a remarkable capacity to develop resistance mechanisms to all drugs introduced to control it,” said Magnus Unemo, the report’s lead author, of the Swedish Reference Laboratory for Pathogenic Neisseria.

“Japan has historically been the place for the first emergence and subsequent global spread of different types of resistance in gonorrhea,” Unemo said. Historical data suggest that were the H041 strain to disseminate further, it could spread internationally within 10 to 20 years, he said.

Experts say the best way to stop the emergence of resistant strains would be to treat gonorrhea infections with two or more different types of antibiotics at the same time, much as TB is treated.

When asked about the superbug’s susceptibility to the powerful antibiotic class called carbapenems, Unemo replied, “Carbapenems have never been used for the treatment of gonorrhea, so we cannot interpret the data in any reliable or quality-assured way at the moment.” Trials would be needed to assess their strength, he said.


**Haiti Passed Up Cholera Vaccine Offer, Crucell CEO Says**

Ronald Brus, CEO of the Dutch vaccine maker Crucell, said Haiti did not accept an offer of tens of thousands of cholera vaccine doses late last year, the *Financial Times* reports. Brus said Crucell offered significant donations of its Dukoral cholera vaccine, but Haitian health officials passed on the offer, according to the newspaper.
"Peter Graaff, the current Haiti representative of the World Health Organization, said he was unaware of the specific Crucell offer, but that a decision had been taken by the country's health ministry at the time to reject proposals for cholera vaccination," the newspaper writes. Haitian officials did not respond to the Financial Times' requests for comment, "but Jon Weigel from Partners in Health ... who followed the discussions, said the rejection was justified at the time by concerns over the social tensions that could be sparked by distributing limited quantities only to some Haitians" (Jack, 7/10).

In related news, the Associated Press/Seattle Times reports that the number of cholera cases in Haiti has increased recently, "fueled by weeks of heavy rains that have helped spread the waterborne bacteria that flourishes in the country's rivers and rice fields." According to Haiti's health ministry, at least 370,000 people have been sickened by cholera and more than 5,500 people have died from the disease since the outbreak began in October, the AP/Seattle Times reports. "The precise total is unknowable since many Haitians live in remote areas with no access to health care" (Daniel, 7/9).

**Type-3 Poliovirus Case In Pakistan Raises Concerns Disease May Spread, WHO Says**

Pakistan has reported the first case of the type-3 wild poliovirus in six months, raising concerns that the disease may spread to other parts of Asia and beyond, the WHO said on Thursday, Bloomberg/San Francisco Chronicle reports. "Confirmation of continuation of WPV3 transmission in tribal areas of Pakistan has significant implications for the global effort to eradicate WPV3, particularly as Asia is on the verge of eliminating circulation of this strain," the WHO said on its website.

"Nine out of 10 of this year's polio cases were caused by type-1, which the WHO says is the most pervasive strain of poliovirus. Type-2 has been eliminated in the wild, with the last cases detected in India in 1999. Type-3 is localized in northern India, northern Nigeria, Pakistan and Afghanistan, the U.N. agency says," the news service writes (Wadhams/Gale, 7/8).

**Malaria parasites use camouflage to trick immune defences of pregnant women**

Researchers from Rigshospitalet – Copenhagen University Hospital – and the University of Copenhagen have discovered why malaria parasites are able to hide from the immune defences of expectant mothers, allowing the parasite to attack the placenta. The discovery is an important part of the efforts researchers are making to understand this frequently fatal disease and to develop a vaccine.

Staff member at CMP. Photo: Lars Hviid"We have found one likely explanation for the length of time it takes for the expectant mother's immune defences to discover the infection in the placenta," says Lea Barfod, MSc, who is working with Professor Lars Hviid at the Centre for Medical Parasitology, University of Copenhagen.

"The parasites are able to assume a camouflage that prevents their recognition by the immune system antibodies which would otherwise combat them. So although the immune system has all the weapons it needs to fight the infection of the placenta, these weapons are ineffectual simply because the enemy is hard to spot. Ironically the camouflage also consists of antibodies, but of a type that does not help to fight infection."

**The malaria parasite at war with the immune system**

One human being in twelve is infected with malaria. That means 500 million people are carrying the tiny parasite, and it kills a million of them a year. The disease costs so many lives because the parasite constantly outmanoeuvres the human immune system. It starts by hiding in the red blood cells. The immune system does not bother with these as the spleen usually filters defective blood cells.

To avoid this filter, the parasite ejects a protein hook which attaches to the inner wall of the blood vessel, and even if the immune system antibodies destroy one such hook, the parasite has more than sixty in its arsenal. One of them has evolved specially to attach to the placenta. While the war is being waged the parasite propagates and infects more and more red blood cells, which are normally used for transporting nutrients and oxygen around the body.

**Fighting from house to house**

"In an advanced version of hide-and-seek the parasites keep looking for new ways of preventing the antibodies from recognising them. It is a kind of urban guerrilla war in which the fighting is conducted from house to house," says Lars Hviid.

"One example is the ability of the parasites to hide in the placenta. The first time an African woman conceives her placenta provides a new opportunity for the parasite to hide: a new house, so to speak, and in a way that prevents discovery by the immune system. It takes time for the immune defences to react to the new threat, and meanwhile the camouflaged parasite harms the woman and her unborn child."
The researchers are now going to study whether the malaria parasite also uses its camouflage at other stages of an infection.

"Perhaps it is not only the parasites in the placenta that are capable of hiding like this," Lars Hviid says.

"It takes the body a surprisingly long time to develop protection from Malaria, and perhaps the trick we have just discovered is part of the explanation. It is important for us to find out if this is the case in order to help us to understand malaria in general, but also to help us in our efforts to develop a vaccination. We have plenty of work to be going on with," Lars Hviid concludes.

Lea Barfod and Lars Hviid’s discovery has just been published in the *Proceedings of the National Academy of Sciences* of the United States of America.

**Exosome Explosion (long)**

These small membrane vesicles do much more than clean up a cell’s trash—they also carry signals to distant parts of the body, where they can impact multiple dimensions of cellular life.

*By Clotilde Théry | July 1, 2011*

Secreted vesicles known as exosomes were first discovered nearly 30 years ago. But, considered little more than garbage cans whose job was to discard unwanted cellular components, these small vesicles remained little studied for the next decade. Over the past few years, however, evidence has begun to accumulate that these dumpsters also act as messengers, actually conveying information to distant tissues. Exosomes contain cell-specific payloads of proteins, lipids, and genetic material that are transported to other cells, where they alter function and physiology.

Two years ago, I began receiving daily e-mails requesting reprints of my articles on exosomes, details on experimental protocols, and advice on the purification and characterization of the vesicles. Having studied exosomes for more than 10 years, I thought I knew all the other researchers working on the subject, but the requests were from groups I hadn’t heard from before. The flood of inquiries made me realize that the field had been growing, attracting the attention of more and more researchers over a relatively short period of time.

A quick glance at the literature confirmed the trend: while only about 20 PubMed-referenced papers containing the word “exosomes” were published in 2003, and just over 60 in 2007, nearly 500 exosome studies have been published since. To take advantage of this flood of research I organized an international workshop on the subject together with Graça Raposo, who in 1996 discovered exosomes made by immune antigen-presenting cells. A 2005 meeting organized by the late Rose Johnstone, who participated in the first description of exosomes in the 1980s, had drawn 25 scientists to Montreal, Canada; the new meeting, which took place this January at our home institution, the Curie Institute in Paris, attracted nearly 10 times as many attendees. At the meeting, researchers in fields ranging from immunology to neurology and tumor biology presented their recent findings on exosomes and other types of secreted membrane vesicles, including the ability of pathogens to manipulate host exosome activity and the influence of the vesicles on allergies. We also discussed potential clinical applications, such as their use as biomarkers or therapeutic tools.
Exosomes: a history

Exosomes are small in size (around 150 nm in diameter or smaller) and are secreted by most cell types. They are formed inside the cell in compartments known as multivesicular endosomes (MVE), which take up bits of the cytoplasm and its contents into membrane-bound vesicles. MVE were originally thought to merely help traffic extracellular molecules to lysosomes, where they are degraded. But about 25 years ago, researchers described the opposite process—MVE in developing red blood cells fused with the plasma membrane and released their contents, including numerous small vesicles (later dubbed exosomes), outside the cell.

To document this process, researchers cultured immature red blood cells, known as reticulocytes, with radioactive transferrin, or with a radioactive antibody that bound to the surface receptor for transferrin. Every 15 minutes, they fixed subsets of the cells and imaged them using electron microscopy, to follow the transferrin or the receptor as it made its way from the cell surface into the cell via the endocytic pathway, and traveled through different cellular compartments to MVE. The transferrin, still bound to its receptor, was sequestered in small vesicles that formed inside the larger MVE. Surprisingly, the micrographs showed that some of these MVE fused with the plasma membrane and released these small vesicles bearing transferrin and its receptor to the outside of the cell.

But over the next 15 years, exosomes were all but forgotten—until 1996, when Raposo published her discovery that immune cells such as B lymphocytes also secreted exosomes, and that these vesicles carried membrane-bound molecules essential for the adaptive immune response. Two years later, further research demonstrated yet another exosome-secreting cell type: the dendritic cell, whose exosomes carried functional immune agents that could promote induction of antitumor responses in mice. These results laid the foundation for the hypothesis that exosomes could play active roles in intercellular communication, and prompted explorations into their clinical application. They are being tested as a new type of adjuvant therapy for the treatment of nonoperable lung cancer, currently in a Phase II trial led by the Gustave Roussy Institute in France. (Disclosure: The Curie Institute is contributing to the analyses of immune responses.)

Over the past few years, the development of large-scale protein analysis techniques allowed researchers to detail the type of cargo transported by exosomes. Different cell types secrete exosomes that carry specific sets of proteins that differ from the proteins contained in the membrane vesicles released by apoptotic cells, suggesting that exosomes are actively secreted by living cells. The signal for secretion is unclear, though some cell types seem to release these vesicles without any apparent provocation. Other cells, however, such as B and T lymphocytes, only secrete measurable numbers of exosomes when stimulated by the binding of a cell-surface receptor.

Recent studies of exosomes purified in vitro showed that the vesicles can be captured by other cells, thus transferring any information enclosed in and/or on the exosome. Antigen-presenting cells, for example, share captured and digested pathogens via exosomes, increasing the range and intensity of the immune response against the invaders. Other exosome-bound molecules can induce the inactivation or even the death of the target cell they encounter. Some exosomes, for example, display the Fas ligand on their surfaces, which, upon binding to a Fas receptor, also known as the death receptor, initiates apoptosis.

In 2007, a group led by Jan Lötvall in Sweden discovered messenger RNA and microRNA inside exosomes. Moreover, in vitro experiments showed that the mRNA could be translated into proteins in target cells, providing the first demonstration of genetic information transfer by exosomes. This remarkable discovery not only indicates a new form of intercellular communication, but suggests that exosomes could perhaps behave similarly to viruses, in the sense that they bring with them genetic material that is translated to proteins in the cells they “infect.” This discovery, and the concomitant development of research on microRNAs, has sparked the recent boost in the study of exosomes, the surge in publications, and the packed house of researchers eager to share their most recent findings at the International Workshop on Exosomes in January.
The puzzle of purpose
Given their complex structures, exosomes can have a much more potent influence on the physiology of the cells they encounter than single-molecule mediators, such as lipids, hormones, or cytokines. For one, exosomes carry specific patterns of ligands and receptors on their surface, which likely allows targeting of specific cell types bearing the right counterligands. Furthermore, the numerous proteic, lipiddic, and even nucleic acid components they carry can affect multiple signaling pathways inside target cells, while single molecules that bind to a single receptor on the target cell surface will initiate only a single pathway.

Exosomes are secreted by most cell types and contribute to functions including tissue repair, neural communication, and the transfer of pathogenic proteins.

The changes induced by exosomes upon interaction with recipient cells can vary widely depending on the type and physiological state of the secreting cell, and can either help ward off disease or, in some cases, exacerbate it. Mature dendritic cells, for example, secrete exosomes that carry antigens or contain MHC-peptide complexes embedded in their lipid bilayer, and can induce antigen-specific immune responses. On the other hand, exosomes secreted by mouse dendritic cells subjected to immunosuppressive agents in culture can promote immunological tolerance. Similarly, macrophages infected with nonpathogenic mycobacteria release exosomes that have been shown to bear bacterial antigens, which then are taken up by other antigen-presenting cells and promote immune responses. In contrast, exosomes released by macrophages infected with pathogenic strains of mycobacteria inhibit macrophage activation and cytokine secretion, thus dampening the immune responses that would otherwise be induced against the mycobacterial antigens. The pathogen appears to have evolved to advantageously manipulate the host’s immune system at the level of exosome communication, though the details of this subversion remain to be elucidated.

Exosomes secreted by cancer cells carry antigens from the tumors, and can be captured by dendritic cells and used to present tumor antigens that would activate immune cells against the cancer. However, these exosomes also contain various immunosuppressive molecules, which can inactivate T lymphocytes or natural killer cells, or promote the differentiation of regulatory T lymphocytes or myeloid cells, which suppress immune responses. It’s unclear whether the net result of these contradictory effects will be beneficial or detrimental to an individual with cancer. Several groups have suggested that secretion of exosomes by tumors promotes their growth by inhibiting antitumor immune responses, or by promoting angiogenesis or migration to other parts of the body in metastasis. But even if exosomes from tumors are found in the circulation of cancer patients, this could simply be the result of tumor expansion, and may not mean that the membrane vesicles are actively involved in tumor progression. The demonstration of a tumor-promoting function of tumor exosomes in cancer patients is still lacking.

Other tissues or cells also secrete exosomes bearing immunosuppressive molecules. Placenta-derived vesicles found in a mother’s blood, for example, bear inhibitory ligands for natural killer lymphocytes and other immune-system components, which possibly prevent immune attack on the fetus. Similarly, exosomes and other vesicles present in the bronchoalveolar fluid can transfer resistance to an allergen to other animals. When exosomes purified from mice that had been tolerized to an allergen were injected into naïve mice, the allergy-prone mice became resistant to an allergic reaction. On the other hand, exosomes in bronchoalveolar fluid can also increase pro-inflammatory responses, as when exosomes purified from asthma patients are cultured with airway epithelial cells, which respond by secreting pro-inflammatory cytokines. Eukaryotic parasites or pathogens have also recently been found to secrete exosomes, which can contribute either to tolerance of an invader (by dampening immune response), or, conversely, to pathologic inflammatory reactions to its presence.

In addition to the immune system, exosomes probably affect other physiological functions. Exosomes are secreted by neural, epithelial, muscle, and stem cells, and the range of their proposed functions includes contribution to tissue repair, communication within the nervous system, and formation and transfer of pathogenic proteins such as prions and amyloid deposits. Neurons, for instance, secrete exosomes bearing receptors for neurotransmitters, which could thus participate in elimination of the neurotransmitter in the extracellular space to stop signaling, and/or could transfer these receptors to other cells to make them responsive to the neurotransmitter. There is no doubt other systems and functions will appear in the coming years.

Challenges in exosome research
Despite the growing amount of data on the changes induced by exosomes on target cells, all these studies were performed on vesicles concentrated in vitro. In most cases, cultures were held in conditions that minimized cell death to ensure that the analyzed vesicles were not contaminated with random cellular debris spilled out by broken, dying cells. But given this technical challenge, reliable purification of
exosomes from whole organs is still impossible. Mechanical or chemical tissue disruption will necessarily break open some cells, and make it impossible to separate exosomes naturally present in the extracellular space from vesicles artificially released from broken cells.

Furthermore, distinguishing exosomes from other secreted vesicles, called ectosomes, shed vesicles, or microvesicles—which bud directly from the plasma membrane (see above figure)—has been a long-standing challenge for researchers. Like exosomes, membrane microvesicles contain various active molecules, such as cytokines, growth factor receptors, and RNAs, but they also contain compounds that have not been described in exosomes, such as metalloproteases—enzymes that degrade extracellular matrix components and participate in tumor metastasis. Exosomes can be separated from vesicles of different sizes using ultracentrifugation at different speeds, with the larger vesicles pelleting at lower speed than the smaller ones, but similar-size vesicles of different intracellular origins (e.g., exosomes and certain plasma membrane-derived vesicles) are not separated by this method, making it difficult to identify the effects unique to exosomes.

The fact that most exosome studies were conducted in vitro with purified exosomes also makes it very difficult to know whether the quantities of membrane vesicles used to observe the described effects in vitro and in animal models are physiologically relevant. Indeed, some exosome researchers doubt whether the vesicles actually have any physiological functions in vivo.

Answering this question requires tools to inhibit or increase exosome secretion, without affecting secretion of other membrane vesicles, or general secretion of proteins or lipid mediators. Several groups are currently developing such tools, especially by deciphering the molecular mechanisms involved in exosome formation and fusion with the plasma membrane. Not surprisingly, however, a consensus has yet to be reached on these mechanisms. Indeed, depending on the cell type, different molecules have been described in the biogenesis and secretion of exosomes. Researchers have proposed other approaches to clarify the physiological functions of exosomes in vivo, such as generating exosomes with modified expression of functional proteins, or inserting enzymes into exosomes to identify target cells by measuring enzymatic activity. Using these approaches in genetically modified mice will be the next step in attacking these challenges.

Research on secreted membrane vesicles and their roles as intercellular messengers is a very exciting field, with new ideas, hypotheses, and questions coming up faster than answers. The 2011 International Workshop on Exosomes allowed most of the long-term exosome and vesicle aficionados to meet, exchange ideas with many newcomers, and point out current problems in techniques, definitions, and characterizations. A final discussion session ended with the decision to carry on the momentum from this very productive workshop by setting up future annual meetings, virtual spaces to encourage further discussion, and a scientific society dedicated to the study of exosomes and secreted membrane vesicles. To that end, the next workshop is scheduled for April 2012 in Gothenburg, Sweden; a Facebook page (called Exosomes, microvesicles and other secreted membrane vesicles) and a website for comparison of exosome protein and RNA compositions is now up and running, and the rest will hopefully soon follow.

Membrane-bound biomarkers?
The identification of RNA in exosomes and the development of high-throughput techniques for nucleic acid analyses has led to a recent surge in studies reporting sequences of the genetic material present in these membrane vesicles. Not all mRNAs present in a cell end up in exosomes, suggesting that only specific mRNA sequences are packaged inside the released vesicles. However, it still remains to be established whether there is a set of mRNA that is consistently targeted to exosomes of specific cell types, as is the case for exosomal proteins. MicroRNA (miRNA) molecules have also been observed in various exosome preparations, though it is also unclear whether there is specific targeting of miRNA to the secreted vesicles.

Despite the uncertainties about the nature of mRNA and miRNA-carrying vesicles, some biotech and pharma companies have started developing programs designed to use the contents of secreted vesicles as biomarkers for various diseases. RNA molecules encapsulated within membrane vesicles are protected from degradation by RNAses, thus allowing their efficient recovery in exosomes from biological fluids, such as plasma, urine, milk, sperm, or saliva. Ongoing work in different laboratories aims to compare RNA and protein sequences in vesicles isolated from normal and cancer cell lines with those from exosomes found in biological fluids of patients with cancer and other diseases. It is still too early to propose the use of exosomes and their contents as new biomarkers (for either diagnosis, prognosis, or prediction of responses to therapies), but given the current efforts, the next few years will surely determine whether such markers exist and are useful. It is notable, however, that circulating miRNA can...
also be protected from degradation by protein complexes, and the relative importance of protein-protected versus membrane-bound miRNA as markers will have to be evaluated.8

This article is adapted from a review in F1000 Biology Reports, DOI:10.3410/B3-15 (open access at http://f1000.com/reports/b/3/15). For citation purposes, please refer to that version.

References

Embryos Right Genetic Wrongs?
New evidence supports an old idea that embryos with genetic abnormalities can somehow fix themselves early in development.

By Amy Maxmen | July 8, 2011

Embryos whose cells acquire too many or too few chromosomes have a diminished chance of surviving to full term. If they do survive, the abnormal count could result in Down syndrome or another chromosomal disorder. But some of these defective embryos can actually fix their genetic mistakes, according to a study reported last week at the European Society of Human Reproduction and Embryology meeting in Stockholm, Sweden.

The idea was originally proposed in the 1990s, but with little evidence and a lot of skepticism, had quickly fallen by the wayside. The new study garners support for this controversial concept that, if true, is certain to impact patients and doctors involved in the infertility treatment, in vitro fertilization (IVF).

“I think this is an important phenomenon to investigate,” says Nathan Treff, a reproductive geneticist at Reproductive Medicine Associates of New Jersey in Morristown. “But,” he added, “the strength of the evidence must be higher if we are going to help people have healthy children.”

Three days after a woman’s eggs are fertilized in culture, many IVF clinics check to see if the 5 to 8 cells of the embryos have the correct number of chromosomes. If some cells have too few or too many chromosomes, the mother is likely to suffer a miscarriage, and the team may recommend against implanting the embryo.

William Kearns, director of the Shady Grove Center for Preimplantation Genetics in Rockville, Maryland, and his team decided to take advantage of this practice to see if the embryos maintained their genetic defects as they developed. Using SNP microarrays, they reassessed abnormal 3-day-old IVF embryos, which patients had consented to donate to science, two days later. While only a fraction of these abnormal embryos survived those two days, many that did appeared normal.

“To us, this really changes the paradigm for IVF and genetic testing on embryos because most clinics do a biopsy after 3 days, and decide whether or not to discard the embryo,” said Kearns. “This study says maybe we should freeze those abnormal embryos so that they remain in a viable state until we know what our findings mean.”

But such a chromosomal correction might occur remains a mystery. Kearns speculates that the normal cells die or get pushed aside towards a less vital region, such as the placenta, as normal cells divide to form the three germ layers that give rise to the baby itself. Abnormal cells in the placenta would not necessarily kill the fetus, Kearns said. Indeed, investigators reported in 1983 that a small percentage of placental cells have erroneous chromosome counts, leading others to suggest just such an idea, said Joyce Harper, an reproductive geneticist at University College London.

The mechanism by which an embryo could recognize a genetic abnormality and either kill or actively push these cells to the side, however, is a bit hard to imagine, said Mark Martindale, an embryologist at Kewalo Marine Laboratory in Honolulu, Hawaii. “I assume genetic abnormalities would have to be detected on the cell surface, and I have no idea how that would happen at such an early stage.”

Treff questions the validity of the results altogether. He points to the lack of a control, noting that there’s no way to know how accurately Kearns’ microarray technique assessed chromosome number.
Kearns countered that he’s previously validated his technique, adding that researchers simply “don’t have the luxury of using human embryos as controls.”

But Harper thinks the finding is quite likely real. At this point, she said, she’s heard enough presentations about embryos with problems at day 3, which somehow subside by day 5, that clinicians should start taking the hint. “Kearns’s study just confirms what we’ve said for years. Do not genetically test the embryo on day 3,” she said, pointing to a recent clinical trial that showed no increase in pregnancy rates by screening embryos at this stage. She says until there’s evidence of a benefit from clinical trials, counting embryos’ chromosomes prior to implantation need not be done. “It’s just not fair to patients or the to the IVF team to do time-consuming and expensive procedures for no reason. This is a real bee in my bonnet.”

**Putting Vaccines to the Test**

*Gene expression analysis allows researchers to predict which patients will respond to flu vaccines and possibly expedite vaccine development.*

**By Tia Ghose | July 10, 2011**

Measuring gene and protein expression levels throughout the body, researchers can predict who will muster up a rousing immune response to the flu virus just a few days after vaccination, and presumably be better protected against a subsequent infection. The findings, published yesterday (July 10) in *Nature Immunology*, could explain why vaccines work in some patients but not others, and provide general principles to determine which vaccines will be most effective in a given population.

The approach—using system-wide expression data to predict immune response—is new, and could lead to improved vaccine development, said Sanae Sasaki, an immunologist at Stanford University, who was not involved in the study. “If they can find a key factor that is related [to] immune response, maybe they can find an alternative [vaccine] to induce the immune system” in people who do not have a robust immune response.

Vaccine trials are often slow and expensive, because researchers must vaccinate thousands of people and then wait until some get sick to see if the prevention was successful, said Bali Pulendran, an immunologist at Emory University and co-author of the study. Several years ago, Pulendran and his colleagues began wondering whether system-wide gene and protein expression could predict immune response and thus speed up the clinical trial process.

In 2009, the team used gene and protein expression data to predict immune response to the yellow fever vaccine, identifying a suite of specific markers that could forecast the vaccine’s effectiveness in a given patient. But because that vaccine uses a live virus that replicates inside the host body, it wasn’t clear that the same approach would work for inactivated virus or carbohydrate vaccines.

To test these other vaccine types, Pulendran and colleagues took blood samples from 56 healthy young adults who received either an inactivated influenza or a live attenuated influenza vaccine. At 3 days and a week after vaccination, the researchers measured subjects’ levels of gene expression and inflammatory chemicals known to play a role in immune response. They used mathematical modeling to pinpoint changes in several thousand genes, including several B-cell associated genes, in subjects that went on to have more robust antibody production a month later, regardless of which vaccine they had received.

“We initially began having no preconceived ideas of what genes were important, but as this thing progressed, we could come up with signatures that could predict vaccine efficacy,” Pulendran said. In addition, gene expression analyses revealed noticeable differences that could explain why those vaccinated with the inactivated virus mounted a stronger immune response than those who received attenuated live virus.

The new approach could be used to vet early vaccine candidates in small studies before investing in costly Phase III trials, Pulendran said. Furthermore, researchers can use the technique to retrospectively analyze data to see why some patients responded to a vaccine when others didn’t, he added, which may provide clues for improving the vaccine’s efficacy. Ultimately, the team hopes to deduce general principles about the gene and protein expression that signal an effective immune response for a wide variety of vaccines, and is currently studying whether the approach will work for other existing vaccines, including malaria and shingles.

Follow-up work should also test “individuals who are immune-compromised—the elderly, very young children, or infected individuals—where we need to see why vaccines work less well,” added Rafick-Pierre
Sékaly, director of the Vaccine and Gene Therapy Institute of Florida and an author of an accompanying News & Views piece in *Nature Immunology*.


**Gilead Kickstarts Patent Pool for AIDS Drugs**

*Reuters*, (07.12.2011) Ben Hirschler

In a move that may signal a change in how the developing world accesses treatment, Gilead Sciences—the leading maker of HIV drugs—has announced it will share its intellectual property rights with the new Medicines Patent Pool. Gilead is the first drugmaker to sign on with MPP, an initiative of the UNITAID health financing system that is funded by a tax on airline tickets. MPP’s aim is to create a patent pool that licenses technologies to generic drugmakers to make medicines more widely available to poor patients worldwide.

Gilead will allow for generic copies of the HIV drugs tenofovir, emtricitabine, cobicistat, and elvitegravir, in addition to a combination of these drugs in a single pill known as “Quad.” Cobicistat, Quad, and elvitegravir are still in clinical development, and their inclusion should significantly speed the flow of new treatments to the poor.

“Through systematic licensing of intellectual property related to HIV products, people in developing countries will have access to low-cost versions of those products almost at the same time that people in rich countries do,” said MPP Executive Director Ellen ‘t Hoen.

Gilead will receive a 3 percent royalty on generic sales of tenofovir, which is also used to treat hepatitis B, and 5 percent on the other drugs.

‘t Hoen expects other pharmaceutical firms will follow Gilead’s lead. She is negotiating terms for similar deals with Bristol-Myers Squibb, Roche, Boehringer Ingelheim, Sequoia Pharmaceuticals, and ViiV Healthcare, a GlaxoSmithKline and Pfizer joint venture. “The whole field is changing ... there will be more to follow,” she said.

Drugmakers, who previously negotiated voluntary licensing deals on a case-by-case basis, have had difficulty accepting the concept of a “one-stop” pooling system. The US National Institutes of Health was the first organization to join MPP last September.

**Understanding Disparities in HIV Infection Between Black and White MSM in the United States**

*AIDS Vol. 25; No. 8: P. 1103-1112*, (06.15.2011) Alexandra Oster and others

The investigators sought to evaluate several hypotheses for HIV infection disparities between white and black men who have sex with men, including incarceration, partner HIV status, circumcision, sexual networks, and duration of infectiousness. The study design incorporated the 2008 National HIV Behavioral Surveillance System, a cross-sectional survey performed in 21 US cities.

MSM were interviewed and tested for HIV. For previously undiagnosed MSM, logistic regression was used to test associations between newly diagnosed HIV and incarceration history, partner HIV status, circumcision status, and sexual networks (oldest partners, concurrency and partner risk behaviors). For HIV-positive MSM, factors related to duration of infectiousness were assessed.

Among 5,183 previously undiagnosed MSM, incarceration history, circumcision status, and sexual networks were not independently associated with HIV infection. Infection was associated with having HIV-positive partners (adjusted odds ratio=1.9, 95 percent confidence interval=1.2-3.0) or partners of unknown status (AOR=1.4, CI=1.1-1.7). “Of these two factors, only one was more common among black MSM—having partners of unknown HIV status. Among previously diagnosed HIV-positive MSM, black MSM were less likely to be on antiretroviral therapy (ART),” the authors wrote.

HIV infection differences between black and white MSM may partly be explained by less knowledge of partner HIV status and lower ART use among black MSM, the investigators concluded. “Efforts to encourage discussions about HIV status between MSM and their partners and decrease barriers to ART provision among black MSM may decrease transmission,” they noted.

**HPV Infection Highly Prevalent Among Organ Transplant Recipients, Study Reveals**

HPV is known to cause cervical cancer and SCC in the anogenital area and also plays a role in some forms of head and neck cancer. SCC skin cancer is increasing in incidence worldwide and the risk is particularly high in immunosuppressed individuals such as organ transplant recipients in whom rates are 100 times those of the general population.

Researchers led by Jan Nico Bouwes Bavinck and Mariet Feltkamp of Leiden University Medical Center, studied a total of 210 organ transplant recipients with previous SCC and 394 controls without skin cancer. They used cutting-edge technologies to assess the presence of 25 betaPV types in plucked eyebrow hairs with simultaneous detection of antibodies to these viruses in blood.

Results show that BetaPV infection is highly prevalent in organ transplant recipients; 94% of patients without skin cancers carried DNA in eyebrow hairs and 97% in those with a history of skin cancer. Furthermore, concordant presence of DNA and antibodies to the same beta HPV type is associated with increased risk for SCC skin cancer.

"Carriage of beta HPV types (a particular skin group of HPV viruses) is extremely common in immunosuppressed individuals," Feltkamp notes. "Our research findings help to provide a clearer picture of the specific HPV types that may play a part in causing SCC which ultimately may lead to novel preventative or therapeutic interventions."

**Journal Reference:**

**Two studies show that drugs used to treat AIDS can be used to prevent HIV infection, too**

By David Brown, Updated: Wednesday, July 13, 5:01 AM

Two new studies done in three African countries have shown for the first time that AIDS drugs taken daily can cut by more than half a person's chance of becoming infected with HIV through heterosexual intercourse.

The results, announced early Wednesday, provide more evidence that the drugs responsible for saving the lives of millions of HIV-infected people over the last 15 years may also be the most useful tool for preventing new infections.

In the last 12 months, other research has shown that antiretroviral drugs in either pills or vaginal gels can help prevent infection in specific groups — women and male homosexuals. The new studies show the strategy also works in the broad population of heterosexual men and women in Africa, the group by far most affected by the 30-year-old pandemic.

The standard treatment of HIV infection is three or more antiretroviral drugs taken daily for life once the virus has begun to measurably damage the immune system. When used for "pre-exposure prophylaxis" (PrEP) one or two drugs are taken daily.

One of the new studies, conducted in Kenya and Uganda, was stopped a year and a half early because the results were so dramatic. The other, run in Botswana, ended on schedule in the spring. Researchers planned to describe its results at a meeting in Rome next week but moved the announcement up.

The news adds urgency to efforts to provide vast quantities of antiretroviral drugs to the developing world. Today, 6.6 million people there are taking the medicines for infections they have. Someday, a greater number may take them to avert infection. Worldwide, about 34 million people are living with HIV. Two-thirds are in sub-Saharan Africa.

“These results are fundamentally important for HIV prevention, especially in Africa," said Jared Baeten, a physician at the University of Washington who co-directed the study in Kenya and Uganda. “Our biggest challenge now is how do we move from research to getting things out to the general public where they're most needed," said Lynn Paxton, an epidemiologist at the Centers for Disease Control and Prevention who led the Botswana study.

In the University of Washington study, called “Partners PrEP,” 4,758 couples were recruited from nine locations starting in July 2008. In each couple one person was infected with HIV and the other wasn’t. The uninfected partners were randomly assigned to take a drug called tenofovir; or tenofovir and another drug, emtricitabine, which is a combination sold under the trade name Truvada; or placebo. Everyone was counseled on how to avoid infection and was provided condoms.
Through the end of May there’d been 47 infections in people assigned placebo, but only 18 in those taking tenofovir (a 62 percent reduction) and 13 in those taking Truvada (73 percent fewer).

Both women and men were equally protected. The rate of serious side effects was similar in the three arms of the study, although the researchers did not provide details about complications in their announcement.

In the Botswana study, 1,219 men and women were enrolled and assigned to take either Truvada or placebo. Nine taking Truvada became infected compared to 24 taking placebo—a 63 percent reduction in those on the active drug. People taking Truvada had a greater frequency of side effects such as nausea and dizziness.

While the results of the two studies were similar, they differed greatly from one called FEM-PrEP reported earlier this year. In it, 2,000 women in Kenya, Zimbabwe and South Africa took Truvada or placebo, and Truvada provided no protection. The researchers are trying to figure out why.

Baeten believes a big reason his experiment showed promising results is that the subjects took their pills 97 percent of the time. (In the CDC study in Botswana, people took them 84 percent of the time). He speculated that FEM-PrEP failed to show protection because its participants simply skipped too many doses.

“I think adherence is the biggest driver of the difference between our study and theirs,” he said.

The Botswana study cost $31 million, all paid by the U.S. government. The study in Kenya and Uganda had a budget of $63 million provided by the Bill and Melinda Gates Foundation, but all that money was not used because the experiment closed early.

The drugs used in the studies are made by the California biotech company, Gilead Sciences, which donated them for the research.

Last week, Gilead signed an agreement with a Geneva-based organization called the Medicines Patent Pool that will allow generic pharmaceutical companies in India to make cheap versions of tenofovir and emtricitabine for use in 111 low- and middle-income countries even though the drug is still covered by patents in the United States.

**UNAIDS and WHO hail new results showing that a once-daily pill for HIV-negative people can prevent them from acquiring HIV**

*New data from studies in Kenya, Uganda and Botswana confirm major role of antiretroviral medicine in preventing heterosexual HIV transmission*

**GENEVA, 13 July 2011**—Results announced today from two studies reveal that a daily antiretroviral tablet taken by people who do not have HIV infection can reduce their risk of acquiring HIV by up to 73%. Both daily tenofovir and daily tenofovir/emtricitabine taken as preventive medicine (PrEP—pre-exposure prophylaxis) can prevent heterosexual transmission of HIV from men to women and from women to men.

The Partners PrEP trial, conducted by the University of Washington’s International Clinical Research Center, followed 4758 sero-discordant couples (in which one person had HIV infection and the other did not) in Kenya and Uganda. Couples received counselling and free male and female condoms. The uninfected partner took a once-daily tenofovir tablet or a tenofovir/emtricitabine tablet or a placebo pill. There were 62% fewer HIV infections in the group receiving tenofovir and 73% fewer HIV infections in the group that took tenofovir/emtricitabine than in the group receiving the placebo.

The TDF2 trial, conducted by the United States Centers for Disease Control, followed 1200 men and women in Botswana who received either a once-daily tenofovir/emtricitabine tablet or a placebo pill. The antiretroviral tablet reduced the risk of acquiring HIV infection by roughly 63% overall in the study population of uninfected heterosexual men and women.

“This is a major scientific breakthrough which re-confirms the essential role that antiretroviral medicine has to play in the AIDS response,” said Michel Sidibé, Executive Director of the Joint United Nations Programme on HIV/AIDS (UNAIDS). “These studies could help us to reach the tipping point in the HIV epidemic.”

The medicines are available generically in many countries at prices as low as US$ 0.25 per tablet. In November 2010, the iPrEx trial among men who have sex with men in six countries reported a 44% reduction in HIV transmission among those who took a daily tenofovir/emtricitabine tablet.

“Effective new HIV prevention tools are urgently needed, and these studies could have enormous impact in preventing heterosexual transmission,” said Dr Margaret Chan, WHO’s Director-General. “WHO will be working with countries to use the new findings to protect more men and women from HIV infection.”
UNAIDS and WHO have already been working with countries in sub-Saharan Africa, Latin America and Asia to explore the potential role of pre-exposure prophylaxis in HIV prevention. This news will encourage more people to get tested for HIV, discuss HIV prevention options with their partners and access essential HIV services.

It is currently estimated that only about half of the 33 million people living with HIV know their HIV status. An increase in the uptake of testing for HIV would have a significant impact on the AIDS response, particularly if more people gain access to new HIV prevention technologies in light of the new findings.

UNAIDS and WHO recommend that individuals and couples make evidence-informed decisions on which combination of HIV prevention options is best for them. No single method is fully protective against HIV. Antiretroviral drugs for prevention need to be combined with other HIV prevention options. These include correct and consistent use of male and female condoms, waiting longer before having sex for the first time, having fewer partners, medical male circumcision and avoiding penetrative sex.

Global Health Community Reacts To CIA's Faux Vaccine Operation In Pakistan

After the Guardian broke the story that the CIA organized a fake vaccination program in Pakistan in an effort to confirm the location of Osama bin Laden and obtain DNA from his family members, several writers and health experts reacted to the situation, noting the possible implications for future health efforts.

- On the "Global Health Policy" blog, Charles Kenny, a senior fellow at the Center for Global Development, points out that Pakistan "is in the midst of another polio outbreak, battling to stamp out the disease by next year as a vital part of the global eradication program" (7/12).
- "I am glad we got bin Laden. But doesn't the CIA have enough credibility problems? Was adding to the frenzied fear of conspiracy, not to mention the doubts people have about their leaders or the burdens of physicians who spend endless hours trying to convince reluctant parents to vaccinate their children, genuinely necessary here?" writer Michael Specter writes on the New Yorker's "News Desk" blog (7/12).
- "I think this is a horrible move with potentially dangerous consequences," author Seth Mnookin writes on the PLoS blog, "The Panic Virus." He adds: "We've already seen polio eradication efforts hindered by rumors that the polio vaccine is being used by Western imperialists to sterilize Muslims. Now, anti-vaccine activists have been given a legitimate reason to question the motives behind grass-roots vaccination campaigns" (7/12).
- "What is most concerning to me about this ruse is the wider context in which this operation was conducted. Yes, I am glad that bin Laden is no longer of this earth, but I wonder how many parents in Pakistan will now refuse to get their children vaccinated – particularly against polio?" Managing Editor Mark Goldberg writes on "U.N. Dispatch" (7/12).
- "The phony vaccination program is a grim reminder of the complexity of international relations as well as the interrelatedness of the world. The local doctor leading the program, Dr. Shakil Afridi, 'used a team of nurses and other health workers to administer hepatitis B vaccinations throughout Abbottabad.' He since has been imprisoned by the Pakistanis for his complicity with the American ruse," Kent Sepkowitz, an infectious disease specialist, writes in the Daily Beast. "Yet one could argue that our attention has been focused on the wrong enemy: in the year 2000, 620,000 people died of complications related to hepatitis B, something Dr. Afridi’s vaccinations (were they real) could have prevented. Hepatitis B – now that is a real evil-doer" (7/12).
- Reporter Tom Paulson also rounds up some commentary on the situation on KPLU’s "Humanosphere" blog (7/12).

New study confirms the existence of 'trial effect' in HIV clinical trials

A press release from PLoS ONE

A new study by investigators from the University of North Carolina at Chapel Hill School of Medicine has confirmed the existence of a "trial effect" in clinical trials for treatment of HIV.

Trial effect is an umbrella term for the benefit experienced by study participants simply by virtue of their participating in the trial. It includes the benefit of newer and more effective treatments, the way those treatments are delivered, increased care and follow-up, and the patient's own behavior change as a result of being under observation.
“Trial effect is notoriously difficult to test,” said Prema Menezes, PhD, assistant professor of medicine at UNC and lead author of the study. “Our study used the objective finding of viral load to test our hypothesis,” she said.

Researchers compared viral suppression among patients who began highly active antiretroviral therapy (HAART) in a clinical trial with patients who received HAART in routine clinical care in two different time periods, 1996-1999 and 2000-2006. They found clear evidence of a trial effect during the earlier period, but not during the later period. Researchers offer that improvements to antiretroviral therapy (fewer pills and fewer side effects), and the change in attitude to HIV, which has come to be seen by many as a chronic, but treatable infection, may be among the explanations for the lack of demonstrable trial effect in the later period.

“This is the first study to clearly demonstrate a trial effect in HIV clinical trials, and this has important implications moving forward,” Menezes said. Documentation of a clinical trial effect should be considered when interpreting the generalizability of clinical trial results. At the same time, the fact that no trial effect was observed in the current HAART period argues that the efficacy demonstrated in clinical trials is likely to predict the effectiveness of the therapy in broader treatment populations. Clinicians and public health officials may have increased confidence that treatment guidelines based on clinical trial data are relevant to routine clinical care.

The study was published in the July 13, 2011, issue of the online journal *PLoS ONE*. Co-authors on the study were Joseph J. Eron, MD, William Miller, MD, David Wohl, MD, Peter Leone, MD, and Ada Adimora, MD, all of the UNC School of Medicine.


**July 13, 2011**  
**Study Finds Structural Factors Integral to Understanding Girls’ Vulnerability to HIV in sub-Saharan Africa**

A new study led by researchers at the Johns Hopkins Bloomberg School of Public Health shows that community members correlate an increase in HIV vulnerability among adolescent girls with weak structural support systems. While adolescent girls are three to four times more likely than adolescent boys to be living with HIV/AIDS in sub-Saharan Africa, few studies have examined the reasons community members believe girls are so vulnerable to HIV. The findings are published in the journal *Social Science & Medicine*.

Carol Underwood, PhD, lead author of the study and assistant professor at the Bloomberg School of Public Health’s Department of Health, Behavior and Society, explained, “This study represents one of the few efforts to explore community members’ perceptions of vulnerability to HIV. It is unique because it offers insights into developing an HIV response that is grounded in the views of communities most affected by HIV/AIDS rather than a response based primarily on perspectives from the outside.”

Underwood directed the Gender Initiative on Girls’ Vulnerability to HIV (Go Girls! Initiative), an intervention informed by this study and carried out by the Bloomberg School of Public Health’s Center for Communication Programs. The Go Girls! Initiative used focus group discussions with adolescent girls and boys, adult men and women and community opinion leaders, in Botswana, Malawi and Mozambique to develop social, gender, and behavior change communication approaches to reduce adolescent girls’ susceptibility to HIV infection.

The study found that structural factors, especially insufficient economic, educational, socio-cultural and legal support for adolescent girls, were identified as the root causes of girls’ vulnerability to HIV through exposure to unprotected sexual relationships, primarily relationships that are transactional and age-disparate. This finding is in line with current HIV prevention practice, which advocates for combination prevention that comprises biomedical, behavioral and structural interventions.

“Nevertheless, while greater attention is being paid to the importance of structural interventions in HIV prevention efforts,” cautions Underwood, “most efforts still focus on the individual and disregard the complex socio-economic context where the infections are occurring, a situation which must be met with nuanced and multi-level responses.”

“We found that both adolescents and adults in HIV-affected communities highlighted structural interventions, behavioral interventions, and testing—in that order—for prevention,” she said. Community members explicitly called for policies and interventions to strengthen cultural, economic, educational and legal structures to protect girls, findings that were used to develop the interventions implemented by the Go Girls! Initiative.
When Flu Strains 'Hook Up' Dangerous Progeny Can Result, Says New UMD-Led Study

COLLEGE PARK, Md. – A new University of Maryland-led study finds that 'sex' between the virus responsible for the 2009 flu pandemic (H1N1) and a common type of avian flu virus (H9N2) can produce offspring—new combined flu viruses—with the potential for creating a new influenza pandemic.

Of course, viruses don’t actually have sex, but University of Maryland Virologist Daniel Perez, who directed the new study, says new pandemic viruses are formed mainly through a process called reassortment, which can best be described as viral sexual reproduction. "In reassortment, two viruses enter the same cell; their genetic material is mixed; and new genetically distinct viruses emerge,” explains Perez, an associate professor in the VA-MD Regional College of Veterinary Medicine, Maryland Campus.

According to Perez and his colleagues many factors are involved in the viability of new viruses that result from reassortment, but the most important is the compatibility of their two sets of viral genes to work together to form functional offspring. The importance of reassortment in the generation of viruses with pandemic potential, the scientists say, was demonstrated in 2009 when a novel H1N1 influenza (pH1N1) virus caused the first influenza pandemic in 40 years. That virus was identified as the product of a three way reassortment, between avian, swine, and human influenza viruses.

In their current study, the researchers looked at the compatibility of the 2009 pandemic pH1N1 virus—which has some genetic characteristics that may allow it to reassort more easily than other influenza viruses—with an influenza strain known as H9N2.

Published in the Proceedings of the National Academy of Sciences (PNAS) the week of July 4-8, this new research builds on earlier findings by Perez and his team of the heightened communicability of the H1N1 virus as well as their work on the airborne communicability of H9N2. And it adds knowledge that may advance modern medicine’s longstanding effort to learn how to predict when pandemic flu viruses will arise. An effort that in recent years has focused on study of H5, H7, and H9 subtypes of flu viruses because these all occasionally infect humans and, in the case of H5 viruses, can cause significant disease and death.

For their PNAS study, the researchers created four reassortant viruses with one or two genes from the H9N2 virus and the rest of the genes from pH1N1. They used two different H9N2 viruses to provide the genes. One was a typical H9N2 isolated from a bird in Asia. The other was an avian isolate that had been adapted to infect and transmit in mammals.

Perez and colleagues looked at the growth characteristics of these four viruses and also their infectivity and transmissibility in ferrets. Ferrets are used as a model for human infections as they are susceptible to the same viruses and show similar signs of infection. All four viruses were able to grow to relatively high levels in cell culture. Similarly all four viruses infected ferrets and showed similar signs of disease and levels of replication. Additionally, they were all able to transmit to ferrets housed in the same cage and allowed physical contact. Finally, three of the four viruses were able to transmit to ferrets that were physically separated but shared the same air.

The new results are important for several reasons according to Perez. "Ours is the first study to show respiratory transmission of an H9 reassortant virus in mammals without prior adaptation. This is important because a new virus must be able to transmit via the respiratory route to impact the human population significantly. Secondly, adapting some of the genes to mammalian hosts allows for more efficient infection and transmission. Finally, these studies indicate that the pH1N1 and H9N2 influenza subtypes are highly compatible for reassortment with each other. And this compatibility means there is potential for the emergence of an H9 influenza pandemic."

Oral Sex Expected of Generation Y: Survey

The Age (Melbourne) (06.27.2011) Michelle Griffin
Surveys of sexual health attitudes show oral sex is increasingly common among Generation Y women.
Family Planning New South Wales (FPNSW) finds half of 250 surveyed females ages 16-25 reported having sometimes been pressured to give oral sex; many said young men “expect” it. “Most people I know that have oral sex only do it because everyone else does, and if you don’t, you’re frigid,” said one 16-year-old girl.

Overall, 82 percent said they found oral sex “enjoyable and rewarding,” with the most common reason for having it that “it feels good.” A quarter of the females saw oral sex as a less intimate alternative to penetrative sex, for which they said “they weren’t ready.” Fourteen percent said they considered oral sex safer than other acts.

Contrary to popular belief, the survey found young women do not get information from movies, TV or pornography: 48 percent reported talking to their friends about oral sex, and 32 percent learned about oral sex from magazines. The results were reported in the journal Youth Studies Australia.

The FPNSW findings are similar to those of the national survey of high school students by La Trobe University’s Australian Research Center in Sex, Health and Society. In 2008, 57 percent of respondents in that survey reported having had oral sex by their senior year.

Lynch Vetoes N.H. Bill on Objectionable Materials
*Associated Press*, (07.13.2011)
Saying it would have given the parents of every student veto power over every lesson plan, Gov. John Lynch on Wednesday vetoed a bill that would have allowed parents to object to school materials and request alternative instruction. Under the legislation, the parents and the school district would have been tasked with agreeing on a plan to meet state requirements in the particular subject area, with parents paying the additional expense. Lynch’s veto message noted that state law already allows parents to remove their children from classes for certain lessons on health and sex education. The new legislation failed to define clearly what material would be objectionable, Lynch said, and would be disruptive and difficult to administer.

Horn Of Africa Nations Risk 'Massive Famine,' Shah Says
The nations in the drought-stricken Horn of Africa "are at risk of 'massive famine,' Rajiv Shah, the administrator of the U.S. Agency for International Development (USAID), told the Huffington Post Wednesday." "It's very severe," Shah said. "We know from the data that we've been collecting that this is the worst drought in 60 years and it's going to have severe consequences. Eleven and a half million people are at real risk of malnutrition and famine already," the Huffington Post reports (Hersh, 7/13).

On Wednesday, the International Committee of the Red Cross said in a statement that "[i]n some parts of Somalia, the number of children with severe acute malnutrition has almost doubled since March" and the "[l]evels of malnutrition have reached a new peak and are currently the highest in the world," Reuters reports (7/13).

UNICEF on Wednesday resumed airlifts of aid into parts of Somalia that are controlled by the militant group al-Shabab, after suspending air deliveries in 2009 because of threats from the group, VOA News notes (7/13). The World Food Program on Wednesday "said it could return to the south 'if conditions allow and if the necessary security clearance from the United Nations is granted,'" Reuters writes (7/13).

CDC Investigators Working To Understand Nodding Syndrome Among East African Children
*Nature News* examines the work of a CDC team working in South Sudan, Tanzania and Uganda to investigate nodding syndrome, "a poorly understood and seemingly growing problem in eastern Africa."

The disease, which has struck thousands of children between the ages of five and 15 in the region, "impairs both physical growth and cognitive development" and is marked by head nodding that "occurs when abnormal brain activity causes a brief lapse in neck muscle tone, causing the head to fall forward," the news service notes. Affected children stop eating, are prone to accidents, and many stop going to school or are “isolated because of fears of contagion,” according to Nature News. "Once they have it, they are going to die with it, and much earlier than they would have otherwise," Scott Dowell, director of the CDC’s Division of Global Disease Detection and Emergency Response (GDDER), said (7/13).
UCSF confirms first adenovirus to jump between monkeys and humans

A novel virus that spread through a California monkey colony in late 2009 also infected a human researcher and a family member, UCSF researchers have found, the first known example of an adenovirus "jumping" from one species to another and remaining contagious after the jump.

In a study by the UCSF Viral Diagnostics and Discovery Center, which identified the new virus at the time of the outbreak, researchers confirmed it was the same virus in the New World titi monkeys and the two humans. They also confirmed that the virus is highly unusual in both populations, suggesting that it may have originated from a third, unidentified species.

The direction in which the virus spread, however – from monkeys to humans or vice versa – remains a mystery.

Findings appear in the July 14 issue of *PLoS Pathogens*, a weekly journal of the Public Library of Science, and can be found at [http://dx.plos.org/10.1371/journal.ppat](http://dx.plos.org/10.1371/journal.ppat).

Adenoviruses naturally infect many animals, including humans, monkeys and rodents, and are known to cause a wide range of clinical illnesses in humans, from cold-like symptoms to diarrhea and pneumonia. Unlike influenza or coronaviruses, adenoviruses had not been known to spread from one species to another.

"Now adenoviruses can be added to the list of pathogens that have the ability to cross species," said Charles Chiu, MD, PhD, an assistant professor of laboratory medicine and infectious diseases at UCSF and director of the viral diagnostics center. "It's been hinted at before, but this study is the first to document these viruses crossing the species barrier in real time."

The virus, which researchers have named titi monkey adenovirus (TMAdV), infected more than a third of the titi monkeys in the California National Primate Research Center (CNPRC) in late 2009. In the monkeys, the virus was devastating, causing an upper respiratory illness that progressed to pneumonia and eventually killed 19 of the 23 monkeys (83 percent) that became sick, including healthy young adult monkeys.

Around the time of the outbreak, a researcher who was taking care of the sick monkeys also developed an upper respiratory infection, with fever, chills and a cough that lasted four weeks, as did two members of the researchers' family who had no contact with the monkey colony. All three recovered fully without medical treatment.

The primate center called Chiu when the illness spread through the colony to help identify the pathogen and prevent its spread to other animals. The UCSF Viral Diagnostics and Discovery Center specializes in using a microarray Virochip technology developed at UCSF to identify viruses affecting humans, animals, insects or plants.

Because the researcher's illness was not reported for several months, the virus could no longer be detected directly, so Chiu worked with the California Department of Public Health to conduct antibody testing on the monkeys, the researcher and two of the researcher's family members who also reported having been sick.

Antibodies are a product of the body's immune response to pathogens and generally remain in the bloodstream for several months after infection. As a result, they serve as a marker of whether a person was exposed to a specific virus. Both the monkeys and researcher tested positive for antibodies to the TMAdV virus, as did one of the two family members. No other humans at the center were found to have been infected.

The UCSF team found that the new virus clearly belonged to the adenovirus family, yet was unlike any adenovirus ever reported to infect humans or monkeys, including from large-scale studies by public health agencies such as the U.S. Centers for Disease Control and Prevention. The new virus was so unusual, in fact, that it shares only 56 percent of its DNA to its closest viral relative.

"This is clearly a new species of adenovirus and it's quite different from anything we've seen previously," said Chiu. "Given the unusually high fatality rate of TMAdV in the titi monkeys, they are not likely to be the native host species for this virus. We still don't know what species is the natural host."

Chiu said the lack of previous records of this virus in humans indicates that it is also unlikely to have started with the researcher. In testing other monkeys at the primate center, the team found one healthy rhesus (Old World) monkey with antibodies to TMAdV, which Chiu said could indicate that the virus originated in Old World monkeys, then spread to the New World colony that lacked antibodies against it.

The viral center is conducting further studies in both humans and monkeys in Brazil and Africa to determine whether the virus is common in wild populations of either Old World or New World monkeys, and whether it has crossed species in those settings to humans who live nearby.
A Closer Look at the Placebo Effect

ScienceDaily (July 13, 2011) — Placebos are "dummy pills" often used in research trials to test new drug therapies and the "placebo effect" is the benefit patients receive from a treatment that has no active ingredients. Many claim that the placebo effect is a critical component of clinical practice.

But whether or not placebos can actually influence objective measures of disease has been unclear. Now a study of asthma patients examining the impact of two different placebo treatments versus standard medical treatment with an albuterol bronchodilator has reached two important conclusions: while placebos had no effect on lung function (one of the key objective measures that physicians depend on in treating asthma patients) when it came to patient-reported outcomes, placebos were equally as effective as albuterol in helping to relieve patients’ discomfort and their self-described asthma symptoms.

The study was led by Harvard Medical School investigators at Brigham and Women’s Hospital (BWH) and Beth Israel Deaconess Medical Center (BIDMC) and appears in the July 14 issue of The New England Journal of Medicine (NEJM).

"We were trying to understand whether a placebo effect exists and, if so, whether it was similar with regard to both objectively and subjectively reported measures, and whether similar effects could be observed using different types of placebo," explains lead author Michael Wechsler, MD, Associate Director of the Asthma Research Center at BWH and Assistant Professor of Medicine at Harvard Medical School (HMS).

The study examined 39 patients with chronic asthma who were randomly assigned to undergo treatment with an active albuterol inhaler, with a placebo albuterol inhaler, with sham acupuncture, or with no intervention at all. The researchers administered one of each of the three treatment interventions to each of the study participants, plus a no intervention session, in random order during sequential medical visits (three to seven days apart from each other). The procedures were repeated in two more blocks of visits, such that each patient had a total of 12 medical visits.

At the study's conclusion, findings showed that treatment with the albuterol inhaler resulted in a 20 percent increase in FEV1 (maximum forced expiratory volume in one second ), a measure of lung capacity. This compared with an increase of approximately seven percent in each of the two placebo treatments as well as the "no treatment" control.

"Since there was no difference between either of the placebo treatments and the placebo 'control' [no treatment], we can report that there was no objective placebo effect with regard to change in lung function," says Wechsler.

However, patients' descriptions of their symptoms suggested that a subjective placebo effect does exist: patients reported statistically significant symptomatic improvement with albuterol, as well as with the placebo inhaler and with sham acupuncture. This compared to little improvement, if any, when patients received no treatment at all.

"We chose to study patients with asthma because earlier evidence had suggested that placebos would change the underlying medical problem," explains senior author Ted Kaptchuk, Director of the Program in Placebo Studies at BIDMC and Associate Professor of Medicine at HMS. "While I was initially surprised that there was no placebo effect in this experiment [after looking at the objective air flow measures] once I saw patients' subjective descriptions of how they felt following both the active treatment and the placebo treatments, it was apparent that the placebos were as effective as the active drug in helping people feel better."

These findings, says Wechsler, suggest that physicians and investigators reconsider the implications of subjective, patient-reported outcomes in clinical trials, and consider having a "placebo for the placebo" to monitor a patient's natural history.

"Despite beneficial effects on objective physiological outcome, pharmacologic therapy may not provide incremental benefit on subjective symptoms provided by placebos," Wechsler adds. "But while placebos remain an essential component of clinical trials to validate objective findings, assessment of natural history is essential in the final assessment of patient-reported outcomes."

At the same time, adds Kaptchuk, the study results imply that placebo treatment is just as effective as active medication in improving patient-centered outcomes.

"It's clear that for the patient, the ritual of treatment can be very powerful," notes Kaptchuk. "This study suggests that in addition to active therapies for fixing diseases, the idea of receiving care is a critical component of what patients value in health care. In a climate of patient dissatisfaction, this may be an important lesson."

Journal Reference:
Philippines warns against geckos as AIDS treatment
The Associated Press
10:46 a.m. Friday, July 15, 2011
MANILA, Philippines — The Philippines warned Friday against using geckos to treat AIDS and impotence, saying the folkloric practice in parts of Asia may put patients at risk.

Environmental officials have also expressed alarm about the growing trade in the wall-climbing lizards in the Philippines. An 11-ounce (300-gram) gecko reportedly sells for at least 50,000 pesos ($1,160).

Geckos are reportedly exported to Malaysia, China and South Korea, where they are used as aphrodisiacs and as traditional medicine for asthma, AIDS, cancer, tuberculosis and impotence.

Their use as medical treatments has no scientific basis and could be dangerous because patients might not seek proper treatment for their diseases, a health department statement said.

"This is likely to aggravate their overall health and put them at greater risk," it added.

Treatments for asthma are easily available and affordable, while there are antiviral drugs to control the progress of HIV, it added.

Geckos are carnivorous, nocturnal reptiles from the family Gekkonidae that are found in tropical countries. They are known for their sticky footpads that allow them to climb vertical surfaces, including glass.

Wildlife official Mundita Lim said her office has asked law enforcers to look into the possibility that scammers may have infiltrated the trade because of the exorbitant prices being quoted online by buyers demanding geckos weighing at least 400 grams (14 ounces).

She said geckos in the wild grow up to 200 grams (7 ounces). Those fattened in captivity can grow only up to 300 grams (10 ounces).

In folkloric practice, geckos are dried and pulverized to use as medicine, and there are anecdotal accounts of the saliva or internal organs being collected, according to Lim.

Environment Secretary Ramon Paje earlier warned that collecting and trading geckos without permit can be punishable by up to four years in jail and a fine of up to 300,000 pesos ($6,900).

He said a healthy population of geckos is needed to regulate pests and maintain the fragile ecosystem.

Geckos feed on insects and worms. Larger species hunt small birds and rodents.

July 15, 2011 10:46 AM EDT

STD Rate Twice as High in Older Women: US Study
Agence France Presse, (07.15.2011)
Infection by the single-celled Trichomonas vaginalis parasite is twice as common as previously thought and is particularly prevalent in women over 40, according to a new study.

US researchers presented the findings this week at the 19th Biennial Conference of the International Society for Sexually Transmitted Diseases Research in Quebec City, Canada.

The team, led by Johns Hopkins University scientists, analyzed data from 7,593 US women ages 18 to 89. Using new genetic assay technologies, they found the overall trichomonas infection rate among women was 8.7 percent, compared to previous reports indicating a 4 percent infection rate. The highest rate, 13 percent, was found among women age 50 and older. The infection rate was 20 percent for African-American women, compared to 5.7 percent for white women.

“What we are really witnessing with trichomonas, especially in older women, is that no one ever looked, no one ever tested and diagnosed, and no one is really getting treated, so the infection persists year after year,” said Charlotte Gaydos, senior study investigator.

“And these high numbers really warrant older women getting screened by their family physicians and gynecologists during routine checkups to make sure they are not infected and are not inadvertently spreading it to others,” Gaydos said.

Trichomonas infection may or may not show symptoms. However, it can cause pelvic inflammatory disease, complicate pregnancy and birth, and facilitate the transmission of HIV.

The good news: “Trichomonas infections are quite treatable with antibiotics,” Gaydos said.
The abstract of the report, “Prevalence of Trichomonas vaginalis and Co-infection with Chlamydia trachomatis and Neisseria gonorrhoeae in the USA as Determined by the APTIMA Trichomonas vaginalis Nucleic Acid Amplification Assay,” was published in Sexually Transmitted Infections (2011;87:A72-A73 doi:10.1136/sextrans-2011-050109.113).

**WHO Says World Is Better Prepared For Influenza Pandemic**

"More than 100 public health experts have wrapped up a three-day meeting in Geneva to review a Global Action Plan for Influenza Vaccines that was developed in 2006, and to develop a strategic plan of action for the next five years," VOA News reports, noting that the WHO "says the world is better prepared for the next influenza pandemic than it was in the past" (Schlein, 7/14).

The WHO said on Thursday that international production of seasonal flu vaccine is predicted to double to 1.7 billion doses by 2015, with approximately 37 manufacturers worldwide potentially able to triple that amount to 5.4 billion if a global influenza pandemic occurs, Reuters notes (Nebehay, 7/14).

**Concurrent partnerships in men do not explain HIV incidence in women: number of partners does**

Gus Cairns
Published: 16 July 2011
A study of HIV incidence amongst women in part of KwaZulu Natal in South Africa failed to find any evidence that HIV incidence in women was associated with overlapping, or concurrent, relationships in their male partners.

The study, led by Dr Frank Tanser at the Africa Centre for Health and Population Studies at the University of KwaZulu Natal, was published in The Lancet on July 15.

However the study has confirmed that the more partners women’s male partners have, the higher the HIV risk is to each individual woman. This finding, plus confirmation of a strong association between the number of partners the women themselves had and their HIV infection rate, provides backing for clear and simple partner reduction advice campaigns for both men and women.

**The concurrency hypothesis**

This study’s findings are important because one hypothesis developed over at least the last decade to explain why HIV prevalence is so much higher in southern Africa than elsewhere is that in certain African cultures there is a high prevalence and acceptability, in both men and women, of long-term, concurrent sexual relationships (Halperin 2004 – and see the “Overlapping Relationships” section in Preventing HIV). This is because this pattern maximises the number of people in a community who are sexually connected at any one time.

One mathematical model back in 1997, for instance (Morris) found that when the mean number of concurrent partnerships in a population was 1.68, the largest single sexually-interlinked network comprised 2% of the local population. When the mean number of concurrent partners increased to 1.86, no less than 64% of the sexually-active population became linked into a single network. A real-life study on an island in Lake Malawi (Helleringer) appeared to confirm this.

More recently, however, critics of the concurrency hypothesis (Sawers, Lurie) have asserted that the evidence for an association between concurrency and HIV prevalence is weak.

**Study method**

The new study in The Lancet appears to confirm this, at least as applied to rural KwaZulu Natal, one of the highest HIV prevalence areas in the world.

The problem with establishing or disproving the concurrency hypothesis is that it is not a theory about women’s risk of acquiring HIV, but of their partners’ risk of transmitting it. It does not link sexual risks an individual takes with their risk of infection, but rather links it to multiple risks taken by their partners. A rigorous study would therefore have to measure not only the number of partners women had but the number of partners each one of their partners had, and the degree to which these partners’ relationships overlapped – clearly a huge task.

The Lancet study got round this ingeniously by using the fact that in rural South Africa most people have sexual partners who live very near them: few people see partners who live a long distance away, and in this area, there are relatively few partners who are migrant workers.

It therefore linked men and women not by whether they actually were partners, but by whether they lived in the same location. It broke down a 434 km² area into individual ‘pixels’ with a radius of three kilometres each (28km² in area). It measured HIV incidence in women and the number of partners they had in each micro-area, and also measured in the same micro-area the number of partners men had and whether they had more than one sexual partnership going on at the same time (i.e. concurrency). It then
worked out whether there was an association between the number and concurrency of partnerships in men with HIV incidence in women.

Incidence in women could be established because the area is subject to regular surveillance by the Africa Centre Demographic Information System. This regularly collects HIV risk information and also conducts tests in people over 15 in the area. An estimate of incidence can therefore be made by observing the rate at which people become HIV-positive through successive surveys.

The sexual behaviour data for men, however, were only collected once, in 2004 at the start of the study. Participants were asked how many lifetime sexual partners they had and how many they were currently involved in. If they said more than one, they were regarded as being in concurrent relationships.

**Findings**

This is one of the highest-prevalence areas for HIV anywhere in the world. A quarter of the adult population has HIV, and prevalence peaks at 50% in women ages 25-30 and 44% in men aged 30-35. Overall incidence is 7.5 per 100 people a year and peaks at 7.5% a year in women aged 24 and 5% a year in men aged 29.

Interestingly, marriage was a minority practice in this area, with only 31% of women and 23% of men ever having been married.

Both the average number of partners men had and the average number in concurrent relationships varied hugely by micro-area. The average number of partners men had ranged from 3.4 to 12.9, and the percentage of men involved in concurrent relationships ranged from 4% to 76.3%. In the east of the area, which contained the only semi-urban locale, the township of KwaMsane, men reported high lifetime numbers of sexual partners but relatively few concurrent partnerships; conversely, in the rural west, men reported fewer lifetime sex partners but a higher proportion were in concurrent relationships.

Firstly, the study reconfirmed that there was an extremely strong relationship between more than one sexual partner in women and HIV infection. Computed annual HIV incidence in women reporting no sexual partners in the last year was 0.94% (the average gap between HIV tests was 1.8 years), in women reporting one partner was 4.5% and in women reporting more than one partner was the extremely high figure of nearly 12%.

Secondly, the study found a strong association between the number of partners men had and HIV incidence in women. HIV incidence in women was 3.16% a year in the areas inhabited by the 25% of men with the lowest number of partners, and 4.37% in the areas inhabited by the 25% of men with the highest number of partners. After multivariate analysis, it was calculated that for every increase of one in the lifetime number of partners men in each locale reported, the risk of acquiring HIV in women went up by 8%. This was statistically significant (p=0.004). Women living in areas with men reporting the highest number of partners (over twelve) had nearly double the risk of acquiring HIV compared with women living in areas with men reporting the lowest number of partners (below four).

Thirdly however and by contrast, there was no association seen between concurrency in men and HIV incidence in women. HIV incidence was 3.4% in women in areas where men had the lowest number of concurrent relationships and 3.5% in areas with the highest frequency of concurrency, and there was no association between male concurrency and female incidence (p=0.73).

**Implications and comments**

There are limitations to this study. The men were only asked about the number of partners they had at the start of the study, and this could possibly have changed during the study; and they were only asked whether they were in a concurrent relationship right now, rather than whether they tended to have them. The researchers acknowledge that their findings, featuring a mature epidemic, don’t rule out the possibility that concurrency and therefore highly-connected networks, may have a role to play in the early stages of an epidemic, simply by ensuring HIV reaches more people more quickly.

The researchers point out that their findings provide evidence for the simplest interpretation of the link between multiple partnership and HIV – people with more partners both acquire and transmit it more often – and none for the more complex idea of concurrency. Furthermore, they add, campaigns warning people against concurrency may inadvertently given the impression that “having many serially monogamous relationships does not place an individual at significant risk of infection. “Conversely,” they add, “simplifying the public health message to reduction in multiple partnerships alone is likely to improve message clarity and effectiveness.”

In an accompanying editorial, Nancy Padian of the US Global AIDS Coordinator’s office and Shanthi Manian of the Bill and Melinda Gates Foundation say that this study should serve to inject clarity into messages aimed at African youth.
“Messages should be explicit about the behavioural change required and appropriate for context,” they say.

“Studies...suggest that young people do not understand global catchphrases such as those about faithfulness” and may interpret ‘faithfulness’ as meaning trust rather than monogamy. This study, they add, “reinforces the need for simple, unambiguous prevention messages to discourage individuals from having several sexual partners, whether concurrent or not.”

References

Swazi king endorses mass circumcision in bid to fight HIV
MANKAYANE, Swaziland — Swaziland’s King Mswati III called Friday for his male subjects to get circumcised as he endorsed a campaign aimed at tackling the world’s highest HIV infection rate.

Flanked by a large royal contingent including his mother, who rules alongside him, four of his 13 wives and several children, Africa’s last absolute monarch said men and boys needed to get circumcised to help fight the "terrorist" virus, which infects one in four adults in the kingdom of nearly 1.2 million.

Studies have found men without a foreskin are 60 percent less likely to get HIV, the virus that can lead to AIDS.

"It seems fitting that our men and young boys should be given an initiative that will help them fight this disease," Mswati told a gathering of thousands in the southern town of Mankayane, where he gave his official endorsement to the campaign.

"This virus I shall liken to a terrorist. It is here to finish off our people."

Mswati was entertained by bare-breasted teenage girls, troops of warrior regiments and a military brass band.

Urging his nation to "take care of your lives—stay away from activities that could give you the disease," the king struck a very different note from his pronouncement to parliament a decade ago that HIV-positive people should be "branded and sterilised".

The US-funded circumcision campaign aims to snip 80 percent of Swazi males aged 14 to 49 within a year.

Officials hope to avert 90,000 new infections and save the health system millions of dollars over the next decade.

Circumcision used to be widespread in Swaziland, but was abandoned in the 19th century.

The king likened the return of the practice to other traditions he revived in 2001 as a solution to the rampant epidemic: requiring young girls to wear tassels to display their virginity and banning men from having sex with girls under 18.

When the king broke his own ban by taking a 17-year-old wife, he fined himself a cow.

The US government is spending $30 million (21 million euros) on the campaign—nearly $30 per inhabitant of the tiny kingdom.

"The goal is to have zero new infections by the year 2020," said US Ambassador Earl Irving.

Swaziland has a way to go to reach that goal. Four out of 10 pregnant women test HIV-positive at clinics, Health Minister Benedict Xaba told the media Thursday.

Since the project started six months ago, results have not been encouraging. Only 3,000 have braved the scalpel despite a massive advertising campaign calling on men to "Circumcise and Conquer".

Organisers are pinning their hopes on Mswati, known to his people as "the mouth that speaks no lies", to breathe life into the campaign.

The king still commands enormous respect, but in the rural areas near Mankayane dissatisfaction is bubbling to the surface as his subjects feel the pinch of a deepening economic crisis.

"The king has a lot of money in the bank but he can’t help us. He has many women and a luxurious life. His children get an overseas education. He doesn't care about Swazis," local Boxer Vilakazi told AFP.
"I love the king but 90 percent of youth are not working. Only those close to the king get jobs," said 21-year-old Mthobisi Dlahla, who said he planned to go for the surgery for his own safety—not because Mswati said so.

The polygamous monarch has been criticised for failing to lead by example in his kingdom, where multiple partnerships are seen as the major catalyst of the AIDS crisis.

Mswati did not say Friday whether he intended to get circumcised himself.

The Genome Guardian's Dimmer Switch: Regulating P53 Is a Matter of Life or Death

The team then studied how p53 activation could cause these cells to arrest for too long. Using sophisticated new techniques, they found that p53 lacking its "dimmer switch" turned on too much of a gene called p21, which acts as a brake to halt cells from dividing. "To confirm the significance of that finding, we created mice that expressed the mutant p53, but had only one instead of the normal two

The protein p53 is an important tumor suppressor because it can destroy or halt the growth of cells that develop potential cancer-causing DNA mutations. But as Wahl's lab and others have shown over the past several years, p53 has much broader importance in the life and death of cells. "It's critical for determining whether a cell survives stress and continues to function in a variety of situations," says Wahl.

One problem with p53 is that it apparently evolved to protect the integrity of the genome for future generations, rather than to prolong the lives of individual cells or animals. From the point of view of an animal, p53 sometimes goes too far in killing cells or suppressing growth. Experiments in mice have suggested that even modest reductions in p53's activity greatly increases survival after exposure to radiation, without raising the long-term cancer risk to unacceptable levels.

Scientists therefore are eager to find out how cells naturally regulate p53, so that they can target these mechanisms with drugs. One clue uncovered by recent studies is that regulatory molecules can alter p53 activity by chemically modifying some key amino acids. In the current study, Wahl and colleagues set out to illuminate the function of a stretch of regulatory amino acids at one end of the protein by creating "designer" mice with other amino acids in this region, thereby rendering it inoperative.

The mutant mice had somewhat higher p53 activity than normal mice, at least in some tissues. Based on other studies, Wahl's team expected the mutants to age faster. To their surprise, however, the mutant mice lived about as long as ordinary, "wild type" mice. A second surprise came when Wahl's team exposed the mice to ionizing radiation, of the sort that nuclear power plants may emit. While all the normal mice survived, half the mutant mice died within four weeks.

To understand why the mutant mice died so readily, Vivian Wang, a postdoc in Wahl's lab, collaborated with the Salk veterinarian, Mat Leblanc, and hematologists at UCSD and noted that the irradiated mutant mouse hearts became enlarged and pale, as if they had been starved of oxygen. "Eventually, we found the reason for this," Wahl explains. "We found that irradiation and the ensuing p53 response significantly damaged the blood-forming cells of their bone marrow, but other parts of their bodies seemed quite normal. We followed up these studies with stem cell transplantation experiments to show the mutant p53 really affected the stem cells and their descendents that make the blood."

These results led the team to conclude that the loss of function of p53's normal "dimmer-switch" segment had allowed the protein to become too active in the hematopoietic stem cells of the mutant mice, arresting the stem cells' proliferation and preventing them from replacing the blood cells lost to irradiation. "If the stem cells and their descendents are arrested for too long, they can't recover fast enough, and the mice eventually die of the effects of insufficient oxygenation of critical tissues," Wahl says.

The team then studied how p53 activation could cause these cells to arrest for too long. Using sophisticated new techniques, they found that p53 lacking its "dimmer switch" turned on too much of a gene called p21, which acts as a brake to halt cells from dividing. "To confirm the significance of that finding, we created mice that expressed the mutant p53, but had only one instead of the normal two
copies of p21," Wahl says. "This reduced p21 levels after irradiation. Remarkably, this was enough to significantly reduce the mortality of the 'dimmerless' p53 mice. They were much less sensitive to radiation when they just had one less copy of p21."

The study underscores the importance of an evolutionarily conserved regulatory segment of p53 and the importance of p53 activity in the response to conditions that produce DNA damage. "Our study indicates that the amount of damaged DNA caused by radiation or toxins, isn't the sole determinant of life or death," says Wahl. "The extent to which p53 is also very important."

One implication of this research is that drugs to lower p53 levels, or to reduce its transcription of other growth-stopping genes such as p21, might be used temporarily to reduce unwanted tissue damage from DNA-altering drugs or radiation. Another implication is that p53-boosting drugs, which are currently being tested in cancer patients, could have dangerous side effects if used in combination with other drugs that cause DNA damage. "Our mouse model suggests that if you use a p53-activating agent, the last thing you should do is combine it with a general DNA-damaging chemotherapy or radiotherapy," Wahl says.

Journal Reference:
Breaking the Chain: 'Molecular Cap' Blocks Processes That Lead to Alzheimer's, HIV

ScienceDaily (July 15, 2011) — A new advance by UCLA biochemists has brought scientists one step closer to developing treatments that could delay the onset of Alzheimer’s disease and prevent the sexual transmission of HIV.

The researchers report that they have designed molecular inhibitors that target specific proteins associated with Alzheimer’s disease and HIV to prevent them from forming amyloid fibers, the elongated chains of interlocking proteins that play a key role in more than two dozen degenerative and often fatal diseases.

"By studying the structures of two key proteins that form amyloids, we were able to identify the small chain of amino acids responsible for amyloid fiber formation and engineer a 'molecular cap' that attaches..."
to the end of the fibers to inhibit their growth," said research leader David Eisenberg, director of the UCLA-Department of Energy Institute of Genomics and Proteomics and a Howard Hughes Medical Institute investigator.

The study was published online June 15 in the journal *Nature* and will be available in an upcoming print edition.

"This research is an important first step toward the development of structure-based drugs designed against amyloid disorders," said Eisenberg, who is a UCLA professor of chemistry, biochemistry and biological chemistry and a member of the California NanoSystems Institute at UCLA. "Our results have opened up an avenue so that universities and industry can start creating therapeutics that could not have been produced 10 years ago."

**Toward delaying Alzheimer's disease**

Amyloid fibers are elongated, water-tight structures formed from two linked protein sheets. Proteins from each sheet contribute side chains, causing them to interlock like the teeth of a zipper, Eisenberg said.

The fibers are found not only in Alzheimer's disease but in a variety of conditions, including Lou Gehrig's disease, Parkinson's disease, type II diabetes and a family of disorders related to mad cow disease, among others. In Alzheimer's and other neurodegenerative diseases, the tau protein forms amyloid fibers inside brain cells, destroying them through a mechanism that is still being investigated.

Though many serious diseases are characterized by amyloid fibers, Alzheimer's is the most prevalent, Eisenberg said. Today there are 5 million patients in the U.S. who suffer from Alzheimer's, with 500,000 new cases every year. Alzheimer's health care cost this year alone have been estimated at $178 billion, including the value of unpaid care for Alzheimer's patients provided by nearly 10 million family members and friends.

"By the year 2050, it is projected that there will be 19 million Alzheimer's patients," Eisenberg said. "The care of so many patients with this debilitating illness could be a substantial fraction of the gross domestic product of the United States."

Eisenberg and his research team found that of the entire tau protein, a small chain of just six amino acids—abbreviated VQIVYK—was responsible for the formation of amyloid fibers. By studying the structure of the fibers using microcrystallography, a method developed at UCLA for this research, the team was able to use the fibers as a template to design an inhibitor that could 'cap' the fiber and stop it from growing.

The results were dramatic. The introduction of the inhibitor into a tau protein solution completely prevented amyloid fiber formation, validating the idea that the structure-based design of therapeutics for amyloid diseases is a plausible option.

Despite this success, there is still a long road ahead before a viable therapeutic can be developed to combat the onset of Alzheimer's in human patients, Eisenberg said. The inhibitor, a chain of amino acids, is far too large to penetrate deep into the brain where the tau proteins form amyloid fibers.

"This research is an important step toward identifying smaller molecules that can be utilized to develop a therapeutic," Eisenberg said. "Our goal is to be able to delay the onset of Alzheimer's disease."

**Preventing the transmission of HIV**

Unlike the tau protein, the SEVI (semen-derived enhancer of viral infection) protein is a far more accessible target for a molecular blocker because it builds amyloid fibers in a vaginal environment, a key process in the sexual transmission of HIV, Eisenberg said.

"The presence of SEVI makes the rate of HIV infection through sexual transmission up to 100,000 times more likely," he said. "By blocking SEVI, we have a method for inhibiting the sexual transmission of HIV."

Though the tau and SEVI proteins have different structures and unrelated functions, they both form amyloid fibers with similar morphology, making it possible to design two separate inhibitors using the same process, according to Eisenberg.

The SEVI blocker proved to be equally effective in preventing fiber growth, bolstering the idea that blockers can be designed for other diseases associated with amyloid fibers as well.

"Though many tests remain, it seems we could be on the way to developing a therapeutic," Eisenberg said. "Our hope is that we could make a blocker that could be applied with a vaginal gel or spray that would help to prevent HIV infection."

The tau and SEVI protein inhibitors were designed using synthetic amino acids, similar to the standard protein building blocks of the human body. But these synthetic amino acids were flipped, as if viewed in a mirror, or had added side chains not normally found in nature. Enzymes in the human body
that are programmed to break apart protein-like chains are, in principle, unable to recognize the non-natural amino acids, keeping the blockers safe to latch on to the target proteins.

**Small molecules, big job**

A second research team also led by Eisenberg recently announced that it had identified four small molecules that bind to amyloid fibers, including a promising candidate called 'orange-G' that wedges into the zipper-like fiber and may be able to break it apart.

This study was published June 14 in PLoS Biology, an online journal of the Public Library of Science. "These are the first small molecules visualized as they bind to amyloid-like fibers," Eisenberg said. "These small molecules are less likely to be broken up in the body and can potentially be modified to force apart amyloid fibers or serve as diagnostic tools to identify infected areas of the body."

Eisenberg and his research team found that orange-G was uniquely able to pierce the impenetrable "steric zippers" that seal the water-tight amyloid fibers of the amyloid-beta protein that is responsible for forming senile plaques in Alzheimer's disease.

"In 10 years we have gotten to the point where we are starting to understand the structural biology of amyloid fibers and how to inhibit them and how to interfere with them," Eisenberg said. "The next step is to make practical molecules that inhibit and break amyloid fibers—that is the ultimate goal."

**Journal Reference:**

**Novel Compound Selectively Kills Cancer Cells by Blocking Their Response to Oxidative Stress**

ScienceDaily (July 15, 2011) — A cancer cell may seem out of control, growing wildly and breaking all the rules of orderly cell life and death. But amid the seeming chaos there is a balance between a cancer cell’s revved-up metabolism and skyrocketing levels of cellular stress. Just as a cancer cell depends on a hyperactive metabolism to fuel its rapid growth, it also depends on anti-oxidative enzymes to quench potentially toxic reactive oxygen species (ROS) generated by such high metabolic demand.

Scientists at the Broad Institute and Massachusetts General Hospital (MGH) have discovered a novel compound that blocks this response to oxidative stress selectively in cancer cells but spares normal cells, with an effectiveness that surpassed a chemotherapy drug currently used to treat breast cancer. Their findings, based on experiments in cell culture and in mice, appear online in *Nature* on July 13.

The plant-based compound piperlongumine (PL), derived from the fruit of a pepper plant found in southern India and southeast Asia, appears to kill cancer cells by jamming the machinery that dissipates high oxidative stress and the resulting ROS. Normal cells have low levels of ROS, in tune with their more modest metabolism, so they don’t need high levels of the anti-oxidant enzymes that PL stymies once they pass a certain threshold.

"Piperlongumine targets something that’s not thought to be essential in normal cells," said Stuart L. Schreiber, a senior co-author and director of the Broad’s Chemical Biology Program. "Cancer cells have a greater dependence on ROS biology than normal cells."

Sam W. Lee and Anna Mandinova, senior co-authors from the Cutaneous Biology Research Center (CBRC) at MGH, weren’t looking for a ROS inhibitor when they found PL. Their interest lay in the tumor suppressor gene p53, which is mutated in more than half of all cancer types. Teaming up with the Broad’s Chemical Biology Program and Platform to screen libraries of chemical compounds, they were looking for something that might increase levels of the properly functioning p53 gene.

When they saw a promising signal for PL, they assumed it worked by enhancing the p53 gene. But to their surprise, PL induced cancer cell death independent of the tumor suppressor gene’s activity. And when they tested PL in normal cells, the cells didn’t die.

"The novelty of this compound was that it was able to recognize cancer cells from normal cells," said Mandinova, a Broad associate member and a faculty member at MGH and Harvard Medical School. "It has a mode of action that targets something especially important to the cancer cell."

Their second surprise came after the Proteomics Platform’s quantitative analysis identified the target of PL. The researchers imagined that they might find a protein encoded by a cancer-causing gene was being inhibited in some way, but instead of an oncogene, they saw an indirect process on which cancer cells depend.
A small number of new cancer drugs target oncogenes directly, but this may not be the only promising new direction for treating cancers. Cancer genes do not act alone. PL exploits a dependency that develops after oncogenes transform normal cells into cancer cells.

"Our studies suggest that piperlongumine's ROS-associated mechanism is especially relevant to the transformed cancer cell," said co-author Andrew M. Stern, associate director of Novel Therapeutics at the Broad. "And this in part may underlie the observed selectivity of PL."

The scientists tested PL against cancer cells and normal cells engineered to develop cancer. In mice injected with human bladder, breast, lung, or melanoma cancer cells, PL inhibited tumor growth but showed no toxicity in normal mice. In a tougher test of mice that developed breast cancer spontaneously, PL blocked both tumor growth and metastasis. In contrast, the chemotherapy drug paclitaxel (Taxol) was less effective, even at high levels.

"This compound is selectively reducing the enzyme activity involved in oxidative stress balance in cancer cells, so the ROS level can go up above the threshold for cell death," said Lee, a Broad associate member and associate director of CBRC at MGH. "We hope we can use this compound as a starting point for the development of a drug so patients can benefit."

While hopeful, the authors remain cautious. Much more work needs to be done to better understand how the ROS process differs between normal and cancer cells before clinical studies can even be launched. Further studies will focus on different forms of cancer and their genotypes, or genetic information.

"Our next set of goals is to learn if there are specific cancer genotypes that will be more sensitive to this compound than others," said Alykhan F. Shamji, associate director of the Broad's Chemical Biology Program. "We hope our experiments will help be predictive of whether patients with the same genotypes in their tumors would respond the same way. It would help us to pick the right patients."

Journal Reference:

Bacterial vaginosis raises women’s risk of transmitting HIV
Roger Pebody
Published: 18 July 2011
A man who is in a relationship with an HIV-positive woman has a three times higher risk of acquiring HIV if his partner also has bacterial vaginosis, Craig Cohen told the International AIDS Society conference in Rome today. Whereas it has been previously established that bacterial vaginosis increases a woman's risk of acquiring HIV, this is the first time that it has been shown to increase her risk of transmission to sexual partners.

Bacterial vaginosis (BV) is a condition which occurs when the normal balance of bacteria in the vagina becomes disrupted. This can result in an over-growth of certain bacteria, which may be accompanied by symptoms such as discharge, itching and pain. It can sometimes lead to problems with fertility, childbirth and pelvic inflammatory disease.

A number of prospective studies have established that having BV is associated – for women – with an increased risk of acquiring HIV. Studies on men's risk of acquiring HIV when their sexual partners have bacterial vaginosis have not previously been conducted.

However some studies have shown that BV is associated with an increase of HIV viral load in the genital tract. There is also evidence that HIV-positive women who have bacterial vaginosis when they give birth are at greater risk of passing HIV on to their child.

Craig Cohen presented an analysis of data on couples recruited to the Partners in Prevention study, conducted in seven countries of southern and eastern Africa. There were 2,236 HIV-negative men in the cohort who had an HIV-positive female partner. Both partners were followed for up to two years.

Couples had been together for a median of five years and three-quarters were married. A third reported having unprotected sex, although condoms and counselling were provided by the researchers. The HIV-positive partner had to have a CD4 cell count above 250 cells/mm³ and not be on HIV treatment at the start of the study.

Across over 10,000 study visits at which vaginal flora was assessed, 34.9% of women had bacterial vaginosis, 22.8% had intermediate flora and 42.8% had normal flora.

During the course of the study, 57 of the men became HIV positive when HIV genotyping (env and gag) could confirm that they had similar virus to that of their partner. In other words, they probably hadn’t acquired HIV outside the primary relationship.
The investigators then identified the measurement of vaginal flora for their partner that was taken closest to the estimated date of seroconversion (no more than three months previously). This data was missing for seven women, leaving 50 couples in the analysis.

Nine HIV transmissions originated from women with normal flora, ten from women with intermediate flora and 31 from women with bacterial vaginosis.

After controlling for a large number of potentially confounding factors (sociodemographic, behavioural and biological), men whose partners had BV had a three times higher risk of acquiring HIV than other men. (Hazard ratio 3.06, 95% confidence interval 1.35 – 6.95).

Women with BV did have higher genital viral loads (3.23 log, compared to 3.04 log in women with normal flora). This was statistically significant, but Cohen suggested that it probably isn’t clinically significant.

He advanced two other hypotheses that could explain the increased risk to male partners. Firstly, that normal bacteria may be virucidal against HIV, reducing the proportion of virus that are infectious. Secondly, that bacterial vaginosis could indirectly increase the male partner’s susceptibility to HIV. Cohen noted that long-term sexual partners share genital flora, with men acquiring bacteria from their partners. It is possible, he suggested, that bacteria may activate Langerhans cells and CD4+ T-cells, making the man more susceptible to HIV infection.

**Reference**


**PrEP makes no sense for discordant couples**

First **PReP worked** for gay men, and we were happy. Then **it didn’t work** for straight women, and we were sad. Now, two big studies in heterosexuals have shown it can work for straight couples, and we are deeply confused. Or at least I am.

Taking anti-HIV pills every day cuts the risk of infection by 63%, said CDC researchers in Botswana. It cuts infection by up to 73%, said University of Washington researchers working in Kenya and Uganda. That’s great news, of course.

Here’s why I’m confused. These trials were conducted in “discordant couples” — 1200 of them in one case, and 4758 in the other. That means researchers knew that one person was infected and the other uninfected. They chose to give drugs to the uninfected person, to see if it would stop them becoming infected. And it does, in over 60% of cases. But another recent study shows that if we give the drugs to the infected partner, the one who might actually need these same drugs because they have HIV and need it suppressed, it cuts infection by 96%. So in the case of discordant couples, it seems to make much more sense to give the antiretrovirals in question to the infected partner.

That leaves us with the question: who should get PReP? Right now, there are not enough antiretrovirals to go around to treat all the sick people who need treatment. If we’re going to use them selectively for prevention, we should start with the most effective use, which appears to be early treatment of the infected partner in discordant couples. We could also give them to people who aren’t in a couple but who know that they’re likely to get around a bit and might want to stay safe without using condoms. That’s potentially a lot of people; it will stretch our purses. But more than that, it will stretch our political will. Let’s face it, HIV has reached eye-watering levels in many sub-Saharan African countries because both voters and governments have been in deep denial about their own, and their neighbours’, propensity to have sex with someone who is not their single life-time partner. Some people, including influential religious and community leaders, even continue to believe that giving out condoms encourages licentious sex. To them, giving out ARVs will surely mean encouraging licentious unprotected sex (if you’re anti-condom, is that better or worse?).

So who is PReP for? We’ve got a better option for discordant couples. We’re not going to want to give it to randy adolescents. We know it works for gay men, but some of the countries where the trials took place would rather thump or jail gay men than protect their sexual health. We’ve no idea yet if it works for drug users (though a deeply unethical trial by CDC in Thailand will tell us that soon).

Of course PReP will find its niche; when people actually take it it works really well (though not as well as abstinence, when people actually abstain, or condoms, when people actually use condoms). We’ll find out a bit more about just how well at the annual AIDS circus in Rome next week. I’ll look forward to learning what the actual incidence rates in the studies were, and more about sex differentials and adherence. But I think we would be unwise to rush around talking about massive roll-out of PReP before we actually figure out who it works for in the real world.
As an aside, the results have a huge potential impact for Gilead, manufacturer of both Viread (basically tenofovir, one of the pills that worked in the trial) and Truvada (the tenofovir – emtricitabine combination that was the other). Gilead has come over all generous and has started letting Indian and other developing country companies copy their products. They’ll take a 5% fee; if we really do get for a massive roll-out of PrEP, that will keep drug costs down globally, while giving Gilead extra cash for very little effort. A win-win situation for which they should be congratulated.

**WHO: Blood Tests for Tuberculosis Are Unreliable**
*Associated Press*, (07.17.2011)  Frank Jordans

The World Health Organization said Sunday it will issue guidance against “dangerous” but widely used blood tests to detect TB.

A review of the tests finds they can produce too many false-negative and false-positive results. “The tests are not reliable and a waste of money and time, putting proper care at risk,” said Mario Raviglione, director of WHO’s Stop TB program. They “are in fact dangerous to patients, since some cases will not be detected and some will be called TB when in fact they do not have it.”

The WHO recommendations to be released later this week mark the first time the agency has issued a “negative” policy targeting a particular diagnostic method.

The blood tests are common in developing countries like India, where approximately 3 million people are TB-infected. Worldwide, some 14 million people have the infectious lung disease, and up to a third of the total population is thought to harbor the TB-causing bacteria.

In January, the Lancet reported that some of the blood testing kits are manufactured in developed countries that do not themselves license the tests. Doctors ordering the tests receive a larger commission than they would for ordering the older, more reliable sputum microscopy test, the Lancet said.

“Many of these tests are used in the private-for-profit sector, charging poor people who do not understand the lack of value of the test,” Raviglione said.

**Africans on HIV Drugs Can Expect Normal Lifespan — Study**
*Agence France Presse*, (07.18.2011)

Ugandans with HIV/AIDS who receive antiretroviral therapy (ARVs) can hope to have a near-normal life expectancy, according to research announced Monday at the 6th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention in Rome. The study’s findings are likely applicable elsewhere in Africa, said researchers from the British Columbia Center for Excellence in HIV/AIDS.

The analysis involved data for 22,315 Ugandans with HIV age 14 and older who initiated ARVs between 2000 and 2009. Compared to the average Ugandan life expectancy of 55 years, people with HIV who start ARVs at age 20 could statistically be expected to live another 26.7 years. Those who initiated ARVs at age 35 could live another 27.9 years.

However, life expectancy differed markedly by gender. Beginning ARVs at age 20, a male could expect to live another 19.1 years, while a female could live 30.6 more years. In initiating ARVs by age 35, a male might live 22 years more, though a woman could live another 32.5 years.

It is suspected the gap reflects the tendency of males to access care late in the course of infection. Previous studies have found that earlier ARV treatment is linked to better health.

“The substantial life expectancy afforded by widespread access to [ARVs] underscores the fact that HIV diagnosis and treatment in resource-limited settings should no longer be considered a death sentence,” said lead investigator Edward Mills. “Instead, HIV-infected people should plan and prepare for a long and fulfilling life.”

**An Unexpected Actor in Vaccination: Our Own DNA**
*ScienceDaily* (July 15, 2011) — The teams of Doctor Christophe Desmet and Professor Fabrice Bureau, of the Laboratory of Cellular and Molecular Physiology within the University of Liège’s GIGA-Research centre, and of Professor Ken Ishii at the University of Osaka in Japan have just discovered an unexpected mode of action for the vaccine adjuvant alum. When a vaccine containing alum is injected, contact with alum apparently pushes certain cells of the body to release their own DNA.

The presence of this DNA outside the cells, a place where it is not to be found in normal conditions, thus acts as a stimulant of the immune system and strongly boosts the response to the vaccine.

Alum, a salt of aluminium, is currently by far the most widely used vaccine adjuvant. Developed in the middle of the 20th century, alum has largely demonstrated its effectiveness and safety of use. That it is why
it is found in numerous vaccines. Tens of millions of doses of alum are thus administered each year, and each person in our Western societies has probably received alum at least once in their life. Nevertheless, alum was developed in a relatively empirical manner; the way it helps the immune system to respond to vaccines had not been properly understood up until now.

The discovery by the Belgian and Japanese researchers thus enables a better understanding of the way current vaccines work, and should help in the creation of new adjuvants for future vaccines. The response mechanisms to DNA brought to light in this study could in particular eventually allow the development of new adjuvants with extremely targeted and effective activity.

**Journal Reference:**
Thomas Marichal, Keiichi Ohata, Denis Bedoret, Claire Mesnil, Catherine Sabatel, Kouji Kobiyama, Pierre Lekeux, Cevayir Coban, Shizuo Akira, Ken J Ishii, Fabrice Bureau, Christophe J Desmet. **DNA released from dying host cells mediates aluminum adjuvant activity.** *Nature Medicine*, 2011; DOI: [10.1038/nm.2403](http://10.1038/nm.2403)

**Some cutaneous HPV types may be involved in non-melanoma skin cancer development**

Non-melanoma skin cancer is the most common form of malignancy in adult Caucasian populations, with more than a million cases recorded each year in the USA alone.

**Lifestyle risk factors... but**

The incidence of these cancers is continuously rising due mainly to the aging structure of Western populations, and as a result of growing prosperity, permitting more visits to countries with high sun exposure, which is a key risk factor for NMSC, as well as lifestyle habits associated with prolonged voluntary sun exposure for tanning purposes.

**Immune system disorders also etiological factor for NMSC**

Impairment of the immune system also appears to play an important role in NMSC. Indeed, immunosuppressed organ transplant recipients (OTRs) have a 50-100-fold increased risk of developing NMSC compared to the general population. NMSCs occur 10-20 years earlier in immunosuppressed than in immunocompetent individuals, and the cumulative incidence of skin cancer in patients under immunosuppressive treatment for 10-25 years is approximately 30-40%. Thus, NMSCs cause a severe discomfort in OTR individuals, who often, due to the high number of skin lesions, cannot be treated with conventional surgery.

**Strong suspicion of etiological role for infectious agent**

The link with immune status strongly supports the role of an infectious agent in NMSC. Biological and epidemiological studies indicate that a sub-group of cutaneous human papillomaviruses (HPVs), referred to as beta HPV types, are associated with skin carcinogenesis. However, their direct role in cancer development and in particular whether they synergize with other risk factors, like UV irradiation, remain to be proven.

**DKFZ-IARC collaboration**

In a collaborative DKFZ-IARC program, we have developed a novel experimental animal model to further evaluate the role of beta HPVs in skin carcinogenesis. We have generated transgenic (Tg) mice expressing the viral oncoproteins E6 and E7 from cutaneous beta HPV38 in the basal layer of the epidermis. We found that chronic skin UV irradiation of these transgenic animals promoted the formation of skin lesions that resembled the squamous cell carcinoma (SCC)-precursor lesions in humans, actinic keratosis and subsequently SCC, closely mimicking the scenario observed in humans. In contrast, wild-type mice developed neither actinic keratosis nor SCC when exposed to the same dose of UV. Dr Christopher Wild, Director, IARC, indicated that "[O]ur study shows the existence of a synergy between UV and cutaneous beta HPV in the induction of pre-malignant and malignant skin lesions in this animal model, supporting the further investigation of the role of these viruses in the development of skin cancer in people."

**The way forward: possibilities for action**

"The establishment of the involvement of beta cutaneous HPV types in NMSC development is of paramount importance", continued Dr Lutz Gissmann, Head of the Division of Genome Modifications and Carcinogenesis at DKFZ, "since it may offer the possibility, if causality is established, of novel prophylactic strategies for this disease based on the generation of specific vaccines, as shown for the HPV types associated with cervical cancer". This strategy may be highly beneficial for OTRs, who could be vaccinated before the initiation of the immune suppressive therapy. "However, further research, particularly in humans, is needed in the next decades to understand whether beta HPV prophylactic strategies may possibly have a positive impact on the prevention of NMSC", he concluded.
Hebrew U. scientists identify molecular basis for DNA breakage
Hallmark of cancer cells
Jerusalem, July 19, 2011—Scientists from the Hebrew University have identified the molecular basis for DNA breakage, a hallmark of cancer cells. The findings of this research have just been published in the journal Molecular Cell.

The DNA encodes the entire genetic information required for building the proteins of the cell. Hence, DNA breaks disrupt the proteins and lead to changes in the cell function. These changes can lead to defects in the control of cellular proliferation resulting in cancer development.

Using cutting edge technologies, researchers Prof. Batsheva Kerem and doctoral student Efrat Ozeri-Galai, of the Alexander Silverman Institute of Life Sciences in the Faculty of Science were able to characterize for the first time the DNA regions which are the most sensitive regions to breakage in early stages of cancer development. This is a breakthrough in our understanding of the effect of the DNA sequence and structure on its replication and stability.

"A hallmark of most human cancers is accumulation of damage in the DNA, which drives cancer development," says Prof. Kerem. "In the early stages of cancer development, the cells are forced to proliferate. In each cycle of proliferation the DNA is replicated to ensure that the daughter cells have a full DNA. However, in these early stages the conditions for DNA replication are perturbed, leading to DNA breaks, which occur specifically in regions defined as ‘fragile sites’.

In this research Prof. Kerem and Ozeri-Galai used a sophisticated new methodology which enables the study of single DNA molecules, in order to study the basis for the specific sensitivity of the fragile sites. The findings are highly important since they shed new light on the DNA features and on the regulation of DNA replication along the first regions that break in cancer development.

The results show that along the fragile region there are sites that slow the DNA replication and even stop it. In order to allow completion of the DNA replication the cells activate already under normal conditions mechanisms that are usually used under stress. As a result, under conditions of replication stress, such as in early cancer development stages, the cell has no more tools to overcome the stress, and the DNA breaks.

The results of this study reveal the molecular mechanism that promotes cancer development. Currently, different studies focus on the very early stages of cancer development aiming to identify the events leading to cancer on the one hand and on their inhibition, on the other. The result of the current research identified for the first time DNA features that regulate DNA replication along the fragile sites, in early stages of cancer development. In the future, these findings could lead to the development of new therapeutic approaches to restrain and/or treat cancer.

Reduced viral load reduces HIV risk despite more sex and ‘condom fatigue’ in patients starting treatment in Cameroon

Gus Cairns
Published: 19 July 2011

Results from a study of patients starting antiretroviral therapy in rural hospitals in Cameroon (Cohen) indicate that, while sexual activity increased after the initiation of treatment, and unprotected sex reverted back to baseline after an initial decline, the increase in the proportion of patients with undetectable HIV more than compensated for an increase in otherwise risky behaviour.

The other significant finding in the study was that patients who reported poor communication with their healthcare staff were nearly twice as likely to report not always using condoms while having a detectable HIV viral load, though whether this is cause or effect cannot be shown.

The Stratall ANRS 12110/ESTHER study was a French study of 459 patients, 70 of them women, initiating antiretroviral therapy (ART) in rural hospitals in Cameroon. Its primary aim was to compare clinical outcomes in people randomised either to receive clinical care based on symptoms alone or on symptoms plus laboratory monitoring. Results announced at this year’s Conference on Retroviruses and Opportunistic Infections (Kouanfack) indicated a slight, but significant advantage for laboratory monitoring – see this report for more details.

An important aspect of the Stratall ANRS 12110/ESTHER trial was that sexual behaviour in participants was assessed too. Previously, there have been relatively few studies of the effect of initiating HIV therapy on sexual and risk behaviour of patients in developing countries.

A paper presented at the International AIDS Conference in Vienna last year (Marcellin) found that the proportion of trial participants having sex did increase after the initiation of ART, as did sex with
serodiscordant partners. In this study, sexual behaviour data was collected from 447 of the participants. They found that the proportion of patients reporting sex doubled over the two years of the study from 32% at the start of therapy to 60% two years later. The proportion of participants who had sex involving inconsistent condom use (ICU) with partners not known to be HIV-positive (SD-ICU) was 57% in participants who had not been having sex at baseline and 76% in participants who had.

This raised concerns about the potential for increased access to HIV treatment to restart high rates of HIV transmission. However, this paper did not factor in the reduced infectiousness of patients with viral suppression.

The paper presented this year added this data. It measured sexual behaviour only in patients where full data from every visit both on sexual behaviour and viral load were available, a total of 290 patients. It found that about a third of patients at any one time had a detectable viral load (over 40 copies/ml), with this proportion declining slightly from 37% six months after therapy initiation to 32% two years after.

In common with the Vienna study, it found that the proportion of patients admitting to no or inconsistent condom use (ICU) declined after initiation of therapy from 67% at baseline to 40% at month six but then started increasing again, to 55% at month 24.

Due, however, to the effects of treatment, the proportion of patients who were defined as ‘susceptible to transmitting HIV’ (STH), in other words having ICU while not being virally suppressed, remained steady through the study. While 64% of patients at baseline were in this group, only 23% were at month six and 22% at month 24. Increased levels of sexual activity were therefore balanced out by an increased rate of viral suppression.

The investigators found that treatment reduced an individual’s susceptibility to transmitting HIV by 86% at month six and 89% at month 24.

Other factors related to being ‘STH’ included having more than one sexual partner (2.4 times the risk of being STH) and having sex more than once a week (twice the risk). Another risk factor was ‘limited readiness of health staff to listen’. All of these factors were statistically significant.

The last factor was assessed using a six-point multiple-choice patient questionnaire that asked patients to rate the quality of their relationship with healthcare providers; those rating the poorest quality of communication with healthcare staff were 80% more likely to report susceptibility to transmitting HIV, though from this trial it cannot be shown whether poor communication was responsible for sexual risk or both were symptomatic of underlying factors like depression.

References

Daily aciclovir slows HIV disease progression and reduces viral load
Michael Carter
Published: 19 July 2011
Daily treatment with standard-dose aciclovir delays HIV disease progression and lowers viral load in patients co-infected with herpes simplex virus-2 (HSV-2), results of a study presented to the Sixth International AIDS Conference in Rome show.

The trial was conducted in the Rakai district of Uganda and involved patients with a CD4 cell count between 300 and 400 cells/mm³ who were ineligible for antiretroviral therapy.

Patients treated with aciclovir were 27% less likely to start antiretroviral therapy than those in the placebo arm. The benefits of aciclovir therapy were especially pronounced for patients with a baseline viral load above 50,000 copies/ml.

Presenting the data, Dr Steven Reynolds said the study was looking at “a new treatment strategy for an old drug”.

A large proportion of HIV-positive patients in sub-Saharan Africa are co-infected with HSV-2, and a number of studies have shown that these patients have a higher HIV viral load and faster HIV disease progression than those people without HSV-2.
There has been previous interest in the use of aciclovir to slow HIV disease progression in these patients, and it is known that therapy with this drug can achieve a reduction in viral load of approximately $0.5 \log_{10}$ copies/ml.

Although access to antiretroviral therapy is increasing in sub-Saharan Africa, the majority of patients are not eligible for treatment. Affordable strategies to delay HIV disease progression are needed.

Investigators therefore designed a randomised controlled trial that included HIV/HSV-2 co-infected patients who were ineligible for HIV therapy. On entry to the study, the patients’ median baseline CD4 cell count was 350 cells/mm$^3$ and their median viral load was $4.44 \log_{10}$ copies/ml.

A total of 440 patients were randomised. Patients in the treatment arm received standard aciclovir therapy consisting of 400 mg twice daily. The control arm received a placebo. The study lasted 24 months and the patients underwent detailed monitoring at intervals of six months.

Three per cent of patients were lost to follow-up and 3% died, but study retention was high and excellent treatment adherence was reported.

There were no serious adverse events.

Results clearly showed that therapy with aciclovir slowed HIV disease progression.

Patients treated with aciclovir were 27% less likely than individuals in the placebo arm to experience a fall in their CD4 cell count below 200 cells/mm$^3$ or to develop an AIDS-defining condition and therefore become eligible for HIV therapy (AHR 0.73, 95% CI 0.56–0.97, p=0.029).

Aciclovir therapy was most beneficial for people with a baseline viral load above 50,000 copies/ml, reducing their need to initiate anti-HIV drugs by 38% when compared to the placebo arm (AHR 0.62; 95% CI 0.43–0.96, p=0.03).

However, the benefits of aciclovir for patients with lower viral loads were less clear, reducing their need to start antiretroviral therapy by a non-significant 10%.

Therapy with aciclovir also had a beneficial impact on HIV viral load, which fell by $-0.061 \log_{10}$ copies/ml in patients taking the drug. In contrast, viral load increased by $0.402 \log_{10}$ copies/ml among individuals in the placebo arm.

“Aaciclovir 400mg twice daily delayed disease progression among HIV/HSV-2 co-infected individuals,” concluded Dr Reynolds, who suggested aciclovir “treatment of chronic HSV-2 infection may be warranted in HIV infected individuals”.

He called for further research into the efficacy of the drug, but added that valaciclovir may have an even bigger impact on disease progression.

Reference

South Africa’s PMTCT programme reduces mother-to-child transmission to under 4%
Carole Leach-Lemens
Published: 19 July 2011

Nine years after the start of a national prevention of mother-to-child transmission (PMTCT) programme, South Africa’s mother-to-child HIV transmission (MTCT) rate is under 4% at four to eight weeks after birth, according to South Africa’s first national PMTCT impact evaluation. Results from this evaluation were presented at the Sixth International AIDS Society conference in Rome.

The dramatic reduction is the result of the implementation of a comprehensive national programme to prevent transmission of HIV from mother to infant, through antenatal HIV testing and provision of antiretroviral prophylaxis or treatment for mothers and infants.

There is much documented evidence of the efficacy of PMTCT interventions to reduce perinatal transmissions. However, evidence of the impact and effectiveness of PMTCT programmes at a national level is lacking.

Most high-prevalence countries do not have ongoing country-level monitoring of PMTCT. So the impact of PMTCT programmes on MTCT rates at the population level is unknown; this is the case for South Africa where PMTCT programmes began in 2002.

With international momentum for the elimination of paediatric HIV by 2015, global targets have been set to reduce new paediatric infections by 90% and population-level mother-to-child infection rates to under 5% at 18 months in breastfeeding populations.
Measuring the impact and effectiveness of PMTCT programmes is critical for national programme planning and the eventual elimination of MTCT. No standardised, internationally recognised methods for measuring national mother-to-child transmission rates and PMTCT programme impact exist.

Data from clinical trials provide estimates of efficacy, whereas data from programmes can provide estimates of effectiveness. Transmission rates from clinical data and programme data may appear similar, but it does not mean they can be generalised to all programmes.

One of the key measures of effectiveness is how many complete the PMTCT cascade: from antenatal care, counselling and testing, through starting timely treatment, to returning to test the infant and follow-up care for the infant.

In South Africa, with approximately one million live births annually, coverage of an infant’s first immunisation at six weeks of age was close to 100% in 2010.

The median HIV prevalence rate among pregnant women is 30%, ranging from 17% in the Northern and Western Capes to over 40% in KwaZulu-Natal.

PMTCT is established in close to 100% of healthcare facilities. Distribution of ART is decentralised and nurses are qualified to start people on ART.

To determine national and provincial MTCT rates at four to eight weeks after birth in 2009 and early 2010, and to identify factors contributing to MTCT, the authors undertook a national cross-sectional facility-based survey of 9915 infant-caregiver pairs at their first infant immunisation visit. While South Africa adopted the recommended World Health Organization (WHO) PMTCT guidelines in 2010, this evaluation looked at the effectiveness of the South African 2008 guidelines (Option A) in use at the time.

Data were collected from June 2010 until November 2010, from 565 facilities in all nine provinces. Dried blood specimens (DBS) from the infants were tested for HIV antibodies.

Infants were considered HIV-exposed if born to women who had reported their HIV status and/or their DBS test was antibody-positive; their DBS were tested for HIV infection by DNA polymerase chain reaction (PCR). In total, 30.3% (3003) HIV-exposed infants were identified among the infant-caregivers pairs, of whom 98.5% (2958) had a PCR test result.

One-third (33.9%; 95% CI: 32.0-35.8) of the HIV-infected mothers received triple-drug ART and 20% (95% CI: 18.2-21.8) reported exclusive breastfeeding. The longer and more comprehensive the treatment, the lower were the risks for transmission.

While exclusive breastfeeding and triple-drug antiretroviral treatment (ART) were both protective factors, unplanned pregnancies (AOR=1.7, 95% CI: 0.9-2.9) and mixed feeding (AOR=1.6 95% CI: 1.0-2.5) were risk factors associated with MTCT. Close to two-thirds (62%, 95% CI: 59.9-64.2) of the pregnancies among HIV-infected women were unplanned.

Sixty-two per cent of mothers did no breastfeeding. The presenter, Thu-Ha Dinh, cautioned that this may reduce MTCT but in the long run would increase mortality rates.

The national MTCT rate at four to eight weeks calculated according to population live births was 3.5% (95% CI: 2.9-4.1), while the proportion of infants nationwide that were exposed to the risk of HIV infection during pregnancy or around the time of delivery was 31.4% (95% CI: 30.1-32.6).

Rates varied in the provinces from a low MTCT rate in the Northern Cape (1.7%) and a corresponding exposure rate of 15.6%, to a high of 6% and corresponding exposure rate of 31.1% in the Free State. KwaZulu-Natal, with one of the higher exposure rates of 43.9%, had a relatively low rate of MTCT at 2.8%. These reflect standards of care as well as coverage within the respective provinces.

MTCT rates did not differ according to sociodemographic characteristics, medical care during pregnancy and childbirth, PMTCT knowledge or income.

Dr Dinh noted that limitations of this model included the potential for selection bias. The results are representative of a population who attend primary healthcare facilities. Extremely sick children needing emergency care were excluded from this analysis.

The South African perinatal MTCT rate of under 4% showed low levels of transmission can be achieved, but also highlights the need for follow-up throughout the breastfeeding period.

Given the high uptake of early infant diagnosis (92%) Dr Dinh suggested that a DBS-HIV ELISA test be offered to all infants at routine immunisation services.

Contrary to previous understanding, delivery by caesarean section and having a doctor at delivery were not better options than vaginal delivery or having only a midwife or other healthcare worker in attendance.

Thu-Ha Dinh concluded reducing both unplanned pregnancies among HIV-infection women and mixed feeding have the potential to further reduce MTCT rates.
Small study shows women on stable HIV therapy have very low levels of HIV and high drug concentrations in genital fluids

Gus Cairns
Published: 19 July 2011

A study of paired samples collected from the blood and cervico-vaginal fluid (CVF) of 20 women on stable antiretroviral therapy has found little evidence that there are infectious quantities of cell-free virus in CVF in women on stable therapy.

The study, conducted by Anandi Sheth from the Emory Center for AIDS Research in Atlanta, USA, also found that levels of the drugs studied reached higher levels in the CVF than in the blood – even in one drug, atazanavir, where concentrations had been expected to be lower. This adds to evidence that fears expressed after the FemPrEP study that drugs taken orally might not reach high enough concentrations in the vagina to work as pre-exposure prophylaxis in women may be groundless.

The other interesting aspect of this small study was that samples were taken in the women six times over a four-week period, thus sampling HIV viral load and drug levels at all levels of the menstrual cycle.

All of the women were on a specific antiretroviral regimen of Truvada (tenofovir/FTC) plus boosted atazanavir (ATV/r). All but one of the women was African-American, and all but one had caught HIV through sexual contact. Seventeen of the women were sexually active, 16 with only one sexual partner, and twelve (60%) were in a serodiscordant sexual relationship. They had been, on average, HIV positive for nine years, on their current antiretroviral regimen for 14 months, and had an average current CD4 of 412 cells/mm$^3$.

Counting from the first day of each woman’s period, the first paired blood and cervico-vaginal fluid sample was taken about eight days later or about four days after the end of her period. Samples were then taken every two to four days to a total of six samples over the next four weeks, with the last sample two to three days before the woman started her next period. Between them, the 20 women provided 102 paired blood/genital fluid samples.

Viral load was tested with the Roche Amplicor viral load assay, whose ‘limit of quantification’ (LOQ) is 50 copies/ml in blood and 500 copies/ml in cervico-vaginal fluid. Viral loads below this would conventionally be called ‘undetectable’ but in fact assays like this can detect the presence of lower levels of virus than this, they just cannot quantify the number of copies reliably. Both blood and cervico-vaginal fluid were tested for the levels of both viral RNA, indicating free viral particles, and viral DNA, indicating cell-associated virus.

In blood, cell-associated virus was detected in all samples, simply indicating that proviral HIV was still present in some of the women’s cells despite antiretroviral treatment. Free viral RNA was detected at 58% of visits in 80% of patients. However RNA above the LOQ was only found in 11% of the 102 samples and never found in 60% of patients.

The likelihood of viral RNA being detected (at any count) varied through the month. RNA was detected in 70% of samples provided at the first and second visit, i.e. during the follicular phase when the woman is reaching her peak fertility. In fell to about 50% during later visits, during the luteal phase when fertility is slowly declining.

HIV was less likely to be detected in cervico-vaginal fluid. Cell-associated HIV DNA was detected in 36% of samples, and was never detectable in 30% of patients. Cell-free RNA was detected in 16% of samples and never detected in 55% of patients but no samples of RNA were found where the viral load was above the LOQ of 500 copies/ml. Again, viral levels were higher in the early phase of the menstrual cycle, with RNA found in 25% of the first two samples taken but 10% at later times in the month. However this association with the position in the menstrual cycle was not statistically significant. The only significant predictors of detectable RNA or DNA in cervico-vaginal fluid was the presence of white cells (leukocytes) or blood in the fluid.

Drug levels were higher in all samples of cervico-vaginal fluid than in blood. FTC levels were 12.2 times higher in CVF than in blood and tenofovir levels 3.4 times higher. These levels are roughly in line with previous studies, though somewhat higher (a consensus of results has found that FT levels roughly four times higher in CVF than in blood and tenofovir levels about the same in both body fluids.

The surprise was atazanavir; the consensus of previous studies having been that atazanavir levels are only one-sixth as high in CVF as in blood, whereas in this study they were 2.5 times higher.

Drug levels did not vary by position in the menstrual cycle, or by whether there was detectable virus in the sample.
This was a study of fundamentally healthy women on a stable ARV regimen with apparently 100% adherence. In this population, although viral detectability did vary slightly during the menstrual cycle, 89% of the women were conventionally ‘undetectable’ for HIV in blood and 100% in cervico-vaginal fluid, and all had high drug levels.

While this does not rule out that women in this position may be infectious, especially if infection via cell-associated virus is common, it provides supporting evidence that ARV treatment may reduce women’s infectiousness.

Reference

Bacteria Use Batman-Like Grappling Hooks to ‘Slingshot’ On Surfaces, Study Shows

ScienceDaily (July 19, 2011) — Bacteria use various appendages to move across surfaces prior to forming multicellular bacterial biofilms. Some species display a particularly jerky form of movement known as "twitching" motility, which is made possible by hairlike structures on their surface called type IV pili, or TFP.

"TFP act like Batman’s grappling hooks," said Gerard Wong, a professor of bioengineering and of chemistry and biochemistry at the UCLA Henry Samueli School of Engineering and Applied Science and the California NanoSystems Institute (CNSI) at UCLA. "These grappling hooks can extend and bind to a surface and retract and pull the cell along."

In a study to be published online this week in Proceedings of the National Academy of Sciences, Wong and his colleagues at UCLA Engineering identify the complex sequence of movements that make up this twitching motility in Pseudomonas aeruginosa, a biofilm-forming pathogen partly responsible for the deadly infections seen in cystic fibrosis.

During their observations, Wong and his team made a surprising discovery. Using a high-speed camera and a novel two-point tracking algorithm, they noticed that the bacteria had the unique ability to "slingshot" on surfaces.

The team found that linear translational pulls of constant velocity alternated with velocity spikes that were 20 times faster but lasted only milliseconds. This action would repeat over and over again.

"The constant velocity is due to the pulling by multiple TFP; the velocity spike is due to the release of a single TFP," Wong said. "The release action leads to a fast slingshot motion that actually turns the bacteria efficiently by allowing it to over-steer."

The ability to turn and change direction is essential for bacteria to adapt to continually changing surface conditions as they form biofilms. The researchers found that the slingshot motion helped P. aeruginosa move much more efficiently through the polysaccharides they secrete on surfaces during biofilm formation, a phenomenon known as shear-thinning.
"If you look at the surfaces the bacteria have to move on, they are usually covered in goop. Bacterial cells secrete polysaccharides on surfaces, which are kind of like molasses," Wong said. "Because these polysaccharides are long polymer molecules that can get entangled, these are very viscous and can potentially impede movement. However, if you move very fast in these polymer fluids, the viscosity becomes much lower compared to when you're moving slowly. The fluid will then seem more like water than molasses. This kind of phenomenon is well known to chemical engineers and physicists."

Since the twitching motion of bacteria with TFP depends on the physical distributions of TFP on the surface of individual cells, Wong hopes that the analysis of motility patterns may in the future enable new methods for biometric "fingerprinting" of individual cells for single-cell diagnostics. "It gives us the possibility of not just identifying species of bacteria but the possibility of also identifying individual cells. Perhaps in the future, we can look at a cell and try to find the same cell later on the basis of how it moves," he said.

**Journal Reference:**

**Mechanism Behind Virally-Caused Vomiting Identified**

*ScienceDaily* (July 18, 2011) — Every year, more than 800,000 children in impoverished countries die from diarrhea and vomiting caused by rotavirus and norovirus—'winter vomiting disease'. Researchers at Linköping University and other institutions have now discovered how vomiting develops in viral infections and have found a way to quickly treat these children and others in the risk zone for dehydration.

It is well known that viruses like rotavirus and norovirus are behind the majority of stomach infections. But it was unclear how vomiting developed, and the treatments available were oral fluid replacement and intravenous drips to prevent dehydration of the body.

Now a research team, led by Professor Lennart Svensson at Linköping University, has produced results that show for the first time how the viruses give rise to vomiting. A new treatment is being proposed, with a previously established medicine that is used for nausea and vomiting in cancer treatments. The results are to be published in the online journal *PLoS Pathogens*.

What researchers have found is that the viral infection and the toxin excreted from infected cells stimulate a type of sensory cell called enterochromaffin cells in the walls of the digestive tract. These cells can communicate with the brain via the vagus nerve. "We have shown that the viral toxin stimulates the cells to release serotonin, a signalling substance that in turn activates the brain's vomiting centre," says Maria Hagbom, laboratory engineer in the Department of Molecular Virology at LiU and the chief author of the article in *PLoS Pathogens*.

The pattern was studied both in cell cultures, where the researchers demonstrated that the viral toxin caused a release of serotonin, and in mice, where it was seen that a rotavirus infection in the intestines activated the areas in the brain where the vomiting centre is located.

Cancer patients who suffer from vomiting in connection with cytostatics are treated today with a medicine that blocks serotonin receptors. The researchers' hypothesis is that the same medicine can relieve vomiting caused by rotavirus and norovirus. "The treatment often offered today is fluid replacement, an oral saline and sugar solution which is troublesome with frequent vomiting. Since intense vomiting makes it difficult to retain fluid, this often leads to the patient having to be treated with a drip. Through restricting vomiting with this medicine, many lives in developing countries could be saved," says Lennart Svensson, Professor of Molecular Virology at LiU.

Comprehensive clinical testing is now being planned in Brazil on children infected with rotavirus or norovirus. The hope is that it will start up this fall. If the results are positive, the medicine may come into clinical use in the near future, since it is already approved and established. Beside the clinical study, the research group has established an animal model that is entirely new to Europe for studying illness mechanisms.

**Journal Reference:**
New Suspect in *E. coli* Deaths
Fenugreek seeds are banned in Europe after authorities point the finger at them as a potential source of the deadly *E. coli* outbreak.

By Jessica P. Johnson | July 6, 2011

Fenugreek seeds imported from Egypt are the most likely source of recent pathogenic *E. coli* outbreaks in France, Germany, and several other countries that have killed 49 people, the European Food Safety Authority (EFSA) announced yesterday in a report from its Task Force.

The so-called enterohemorrhagic *E. coli* (EHEC) strain produces Shiga toxins that cause intestinal inflammation and bloody diarrhea. The rare strain (O104) of the *E. coli* bacterium first emerged in May of this year in Germany and, though the number of new cases is decreasing, has since infected nearly 4,200 people in France, Germany, Norway, Sweden, and Switzerland. After fifteen new cases of the rare infection sprang up in France, a joint investigation by EFSA, the European Centre for Disease Prevention and Control (ECDC), the European Commission, the World Health Organization and others traced the source of the bacteria to at least one lot of Fenugreek seeds imported from Egypt. Research is on-going, however, and other sources may be identified, the report noted.

Until further evidence can be gathered, EFSA recommends that consumers do not grow fenugreek seeds for raw consumption or otherwise consume them unless they are well-cooked. The European Union has ordered member states to withdraw fenugreek seed lots delivered between 2009 and 2011 from the EU market and has banned their import from Egypt until at least the end of October.

In related news, the Center for Infectious Disease Research & Policy at the University of Minnesota reports that a company known to distribute fenugreek seeds was initially named in an ECDC risk assessment report published on June 29, but has now been removed. “Some key partners involved felt that it may unnecessarily harm the company to publish its name while the investigations are still ongoing,” explained ECDC spokeswoman Caroline Daamen in an email to the university.

RNAs Regulate Cell Death
Three RNAs expressed in the nucleolus mediate death in cells exposed to too much fat.

By Edyta Zielinska | July 5, 2011

Small nucleolar RNA molecules kill cells exposed to too much fat, according to a paper publishing in the July 6th issue of *Cell Metabolism*. The finding suggests a new role for the RNA molecules, which are known to modify ribosome function, and provides a potential new target for metabolic diseases and complications from diabetes.

“This is a very intriguing observation,” said Barsanjit Mazumder who studies ribosomal modifications at Cleveland State University and was not involved in the research. If confirmed, it would be the first time these RNAs are implicated in metabolic disease.

Even after blood sugar has been appropriately regulated, diabetic patients often suffer from complications, such as heart failure, renal dysfunction and a reduction in the number of B cells in the immune system. Previous research had implicated high fat exposure in cells types that aren’t used to dealing with it, such as heart muscle, or kidney or blood cells, as one possible cause of these complications. So Jean Schaffer from Washington University School of Medicine and colleagues, decided to look for the genetic basis that would explain how excess fat can lead to oxidative stress and eventually cell death.

The authors cultured Chinese hamster ovary (CHO) cells in high fat and then screened for mutants that could survive in the toxic conditions. They then scanned the genomes of the survivors to discover a mutation in a single ribosomal gene that prevented its transcription. But when they inserted a wildtype version of the ribosomal protein into the mutant CHO cells, instead of once again becoming susceptible to the high-fat conditions, the cells survived, indicating that the altered ribosomal protein itself wasn’t causing the fat-resistance.
Schaffer’s team then took a second look at the ribosome’s sequence in the mutant cells and noticed that within the intronic regions of the gene, there were a second set of genes that encode three small RNA molecules that are normally expressed in the nucleolus — the site within the nucleus where ribosomes are translated. The snoRNAs typically help convert newly translated ribosomes into their functional forms, but as a result of the mutation in the ribosomal gene, the fat-resistant mutant cells lacked the RNAs altogether.

Reintroducing the wildtype snoRNAs back into the mutant cells resulted in cell death, suggesting that the presence of the snoRNAs somehow instigated cell death in high-fat environments.

Intriguingly, the effect wasn’t limited to stress from too much fat. When the authors exposed these snoRNA-lacking cells to other types of oxidative stress — such as exposure to hydrogen peroxide, which would kill most cells — they survived, suggesting the RNAs help regulate cell death from a wide range of stressors. However, the authors found that all three snoRNAs were required to restore normal cell death.

Still, some researchers would like more details about how these nucleolar RNAs might be involved in pathogenesis of the disease. “The paper is not telling the mechanism,” said Mazumder. Other lingering uncertainties include why all three RNAs are required, and whether the strong response observed in the CHO cells can be replicated in more physiologically relevant cell-types and animal models. Schaffer’s lab did replicate the experiment in muscle cells and in a mouse model of liver oxidative stress, for example, and found a similar, albeit more modest, effect, said Miriam Cnop, a diabetes researcher from the Universite Libre de Bruxelles. But this observation is just the beginning, said Schaffer. “We’re very curious how these snoRNAs are made in mammalian cells, what are their targets are, and how they contribute to disease processes,” she said.


Placebo of HIV Trials
A new study confirms that a “trial effect” — in which patients improve simply as a result of taking part in a drug study — once existed among HIV trial participants.
By Jef Akst | July 14, 2011

Between 1996 and 1999, HIV patients treated with highly active antiretroviral therapy (HAART) as part of a clinical trial showed greater viral suppression than those patients who received the same treatment in a routine hospital setting, according to researchers at the University of North Carolina School of Medicine, demonstrating that just taking part in a clinical trial was enough to have a positive effect on health outcomes. The documentation of a so-called “trial effect,” which is assumed to be the result of increased care and follow-up as well as changes in the patients' behavior, could impact how researchers design clinical trial and analyze the resulting data.

“Trial effect is notoriously difficult to test,” lead author Prema Menezes said in a press release. “This is the first study to clearly demonstrate a trial effect in HIV clinical trials, and this has important implications moving forward.”

The researchers found no evidence, however, of a similar effect in HIV patients treated with HAART in trials from 2000 to 2006. This difference may be due to an overall change in HIV perception, which has become a very treatable infection, and improvements in the therapy itself, the authors say. Regardless of the explanation, the lack of a trial effect in more recent HIV trials suggests that their results are probably an accurate representation of the treatment’s efficacy, even when administered in a non-trial setting.

A Scar Nobly Got
The story of the US government’s efforts to stamp out smallpox in the early 20th century offers insights into the science and practice of mass vaccination.
By Michael Willrich | July 1, 2011
Our skins record the histories of life’s close scrapes. One of the most common marks that humans carry is, we hope, bound for extinction: the nickel-sized cicatrix left by a successful smallpox vaccination. The deadliest disease in history, smallpox was eradicated worldwide more than thirty years ago. With each passing year, fewer of the world’s inhabitants bear the mark of smallpox vaccination on their arms. Fewer still can remember what those scars once meant. Our fading vaccination scars are not simply a tattooed testament to one of the greatest scientific and medical triumphs of all time. These scars are also a reminder of the shocking level of coercion and harsh treatment once used in vaccination campaigns—and the widespread popular resistance sparked by those measures.

Consider the United States at the turn of the last century, the setting for my new book, Pox: An American History. As smallpox spread across much of the country, infecting and killing thousands, a vaccination scar on the upper arm assumed a new sociopolitical significance. Of course, the mark—a solitary replica of the pitted scars that the Variola virus left upon the faces and bodies of the unvaccinated—had always signified medically administered immunity from smallpox. By 1900 the mark of vaccination, a medical practice already more than a century old, should have occasioned little notice. But as the United States stepped onto the global stage as an imperial power, the most productive industrial economy in the world, and a principal destination for the world’s immigrants, the scar became a badge of “civilization” and citizenship.

Immigrants could not enter the country without one. On US soil, the scar served as a kind of domestic passport, required for admission to many schoolhouses, workplaces, and public spaces. During a smallpox outbreak, anyone who lacked a vaccination scar risked arrest, shotgun quarantine, and, if the person refused to bare an arm for the vaccinator’s lancet, forcible immunization. Seasoned health officers knew better than to trust paper vaccination certificates; they demanded to see the scar. As one writer noted in American Medicine, “This certain, well-defined sign cannot be forged.”

That writer was wrong. As health officials and police aggressively enforced vaccination, resourceful vaccine refusers discovered ways to fake the scars. Some tried plaster counterfeits. Others followed home remedies promoted in unorthodox medical journals. “Get a little strong nitric acid,” advised Medical Talk for the Home. “Take a match or a toothpick, dip it into the acid, so that a drop of the acid clings to the end of the match. Carefully transfer the drop to the spot on the arm where you wish the sore to appear. Let the drop stand a few minutes on the flesh.” After a few minutes, the burning skin turned red—time to blot up the remaining acid. In a week, the spot turned dark. “This sore,” the journal promised, “will gradually heal by producing a scar so nearly resembling vaccination that the average physician cannot tell the difference.” Alarmed health officials condemned such forgeries as a “vile crime.”

As wrongheaded as such resistance may seem today, the public’s wariness of immunizations was often justified: at the time, health officials ordered vaccinations without taking measures to ensure their safety and efficacy. Fortunately, the turn-of-the-century vaccine wars left their marks not only upon the nation’s arms but also on its law books. In order to strengthen public confidence in vaccines, Congress enacted the Biologics Control Act in 1902, establishing a new federal system for licensing and regulating vaccines. American courts issued rulings that placed public health authority on firmer legal ground while also establishing key protections for individuals’ civil liberties. Perhaps most important, popular opposition taught government officials that when it comes to public health, education can be more effective than brute force.

The stories our scars can tell.
Trading Pelts for Pestilence
Researchers trace the evolution and spread of the tuberculosis bacterium back to the early fur trade in Canada.
By Jef Akst | July 1, 2011

When European explorers and fishermen began to frequent Canada’s shores in the 16th century, they brought with them a plethora of tools and trinkets, including knives, axes, kettles, and blankets. The region’s indigenous people traded the Europeans for these items, swapping the one thing they had in abundance—animal pelts. The furs quickly became popular in Europe, and by the early 17th century, the French had established permanent posts in North America to facilitate trade. Little did the natives know that in addition to receiving metal and material goods for their furs, they were also acquiring a strain of *Mycobacterium tuberculosis*, the causative agent of tuberculosis (TB).

The first time Stanford University infectious disease specialist Caitlin Pepperell saw the DNA fingerprints of a sampling of tuberculosis bacteria from Aboriginal peoples in Ontario, she says she “pretty much knew” the bacteria were related to the *Mycobacterium tuberculosis* strains she had studied as part of her research on TB evolution in Saskatchewan. But that didn’t quite make sense. Indigenous communities in the two provinces were more than 1,000 miles apart and were composed of distinct ethnic groups. “I wouldn’t have expected them to be in much contact,” Pepperell says. So how did such isolated groups of people, spread across vast expanses of Canadian territory, come to share a remarkably similar pathogen?

Pepperell contacted researchers around Canada, including Wendy Wobeser of Queen’s University in Toronto, who had sent Pepperell the Ontario fingerprints, to organize a collaborative project to track the evolution of *M. tuberculosis* through Canadian history. Sure enough, *M. tuberculosis* strains from indigenous populations in Ontario, Saskatchewan, and Alberta, as well as strains from French Canadians in Quebec, all appeared to comprise a single lineage, characterized by a shared nitrogenous base deletion called DS6Quebec. The minisatellite data suggested that the bacteria spread among the continent’s Aboriginal populations from a source population in Quebec, accompanying European fur traders as they
set up trading posts further and further west. Historical records show that European immigrants and Canada’s indigenous populations socially interacted, and even intermarried—arrangements which made *M. tuberculosis* transmission likely. Though Pepperell admits that the idea sounded a little “crazy” at first, the more she dug into the data, the more she was convinced that the fur trade was the vehicle for widespread gene flow of a single lineage of *M. tuberculosis* among Canada’s indigenous populations.

“This is a very neat story,” says mathematical biologist Carlos Castillo-Chavez of Arizona State University, who was not involved in the research. “This is almost like the anthropology of disease—the impact of people's mobility and migration patterns on disease evolution.”

“It’s really the most robust description of [tuberculosis] epidemiology in northern Canada,” adds Wobeser, a coauthor of the study, published in a recent issue of *PNAS* (108:6526-31, 2011). Though she suspected the Canadian TB strains were related from the start, she says she wouldn’t have predicted that the link dated as far back as the fur trade. “But now that I know it, it makes sense.”

The data also suggest that *M. tuberculosis* can persist in populations at very low levels for long periods of time, exploding into epidemics as soon as host conditions are favorable. Indeed, though the initial spread of the bacteria likely started as early as 1710, tuberculosis was not commonly seen in indigenous populations until outbreaks in the 19th and 20th centuries.

One possibility for this delay, Castillo-Chavez says, is that the continued colonization of Canada by European settlers disrupted the Aboriginal lifestyle. “This is just a suspicion,” he says, but “my perspective is that TB activation requires some weaknesses in the immune system, and I think that those weaknesses may stem from problems of nutrition”—such as may have occurred as a result of a shift in “the balance of powers” during colonization.

Regardless of the reason, the finding that *M. tuberculosis* can persist at such low levels in the population may explain why the bacterium is so difficult to eradicate, Pepperell says. “Probably the most interesting part is the fact that we can learn so much about the evolution of the bacteria and the evolution of epidemics by integrating this sophisticated genetic analysis with historical research,” she says.

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**Zinc Fingers Bear Fruit**

A method for precise gene editing is able to change disease-causing point mutations in human stem cell DNA.

By Bob Grant | July 18, 2011

Researchers have, for the first time, modified a single, disease-causing mutation without altering any other parts of the genome in human stem cells. Scientists in Rudolph Jaenisch’s lab at the Whitehead Institute for Biomedical Research used zinc finger nucleases (ZFNs) to carefully insert or remove a single base pair in the alpha-synuclein gene—which is known to play a role in Parkinson’s disease (PD)—in induced pluripotent stem (iPS) cells. Such precise and targeted genetic manipulation could help avoid problems associated with messier methods of gene alteration, such as virus-mediated editing, that complicate the use of stem cells as therapeutic agents. “ZFNs can transfer a mutation without any other alterations to the genome, such as leaving in unwanted pieces of DNA that could be harmful,” postdoc Frank Soldner, first author on the paper, published last Thursday in *Cell*, said in a statement. “This precision is ideal for drug research for PD and other diseases, but it is also one more step toward using ES or iPS cells therapeutically.”

Earlier this month, two other postdocs in Jaenisch’s lab used transcription activator like effector nucleases (TALENs), which have gene editing powers similar to those of ZFNs, to precisely and efficiently edit genes in both human embryonic stem cells and iPS cells. That work was published in *Nature Biotechnology*. 
New Flu Vax Same as Old
The 2011 flu vaccine will be based on the same virus strains as last year's vaccine.
By Edyta Zielinska | July 19, 2011
Every year, the government takes a gamble on the strains of flu most likely to cause the greatest number of infections in the coming flu season, and commissions a vaccine based on those strains. The US Food and Drug Administration announced Monday (July 18) that this year's lucky numbers will be the same as last year's, since those strains are still some of the most widely circulating and most frequently associated with disease.

The viruses used are chosen by 136 influenza surveillance centers around the world, whose samples help determine the most prevalent circulating strains. This year’s chosen ones include the H1N1 flu strain responsible for the “swine flu” pandemic of 2009, as well as another type A virus, and one of the two prevalent B type strains.

Although the vaccine composition is the same, the CDC still recommends those who took it last year to get an additional shot, because the vaccine protection may not last as long as a year. For more information, go to the CDC’s FAQ page.

Panel Calling for Free Contraceptive Coverage
Health insurers should be required to fully cover, with no co-pays, eight additional prevention services for women under the federal health care law, says a new Institute of Medicine report. The IOM panel, tasked by the US Department of Health and Human Services (HHS) to recommend preventive services critical to women’s health, focused especially on addressing the gap in reproductive care.

The recommended services include:

- Human papillomavirus DNA testing for women over age 30
- STD counseling
- HIV counseling and screening
- All contraceptive methods approved by the Food and Drug Administration, as well as counseling for patients wishing to prevent unintended pregnancy.

Obama administration officials said they are likely to accept the advice, which, if acted upon by Aug. 1, would take effect for many plans at the beginning of 2013.

Nearly half of all US pregnancies are unintended, IOM noted, and about 40 percent of these end in abortion. Broader contraceptive uptake would reduce teen and unintended pregnancy as well as abortion, it said. While the IOM panel did not consider cost specifically, “contraception is highly cost-effective,” it said.

The US Conference of Catholic Bishops, Family Research Council and other conservative groups denounced the birth control recommendation. Many obstetricians, gynecologists and female Democrats in Congress hailed the proposal.

In creating the list, IOM considered whether a service is supported by high-quality, peer-reviewed studies and systematic reviews, and is identified as a federal priority; and whether it is supported by governmental, professional and reimbursement policies. A service had to affect a broad population; have a large potential impact on health and well-being; and be supported by strong evidence.


Scientists Aim at HIV’s Last Holdout
Agence France Presse , (07.19.2011)
A group of 35 scientists and stakeholders on Monday published “The Rome Statement for an HIV Cure,” which asserts, “Now, more than ever, it is time to seriously start looking for an HIV cure.”

The statement — released in Rome at the 6th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention — kicks off a new global scientific strategy, “Towards an HIV Cure,” which targets the virus’ remarkable resiliency.

The early euphoria that accompanied the 1996 introduction of combination antiretroviral therapy gave way to disappointment when scientists realized HIV could hide in reservoirs inside the body, escaping destruction by the drugs, then rebound when treatment is interrupted.
The statement advocates for the “development of, at least, a functional cure that, without completely eliminating the virus from the body, would permanently suppress its replication and considerably diminish viral reservoirs, possibly leading to the long-term remission of patients.

“Not only would such a strategy act as therapy at the individual level but, considering the growing evidence that HIV transmission is dramatically reduced in the absence of detectable viral load, it would most probably contribute to HIV prevention at the population level,” the statement says.

The new strategy “aims at building a global consensus on the state of HIV reservoirs research and defining scientific priorities that need to be addressed by future research to tackle HIV persistence in patients undergoing antiretroviral therapy.”

“It’s the right moment to stimulate research for an HIV cure, using a multidisciplinary approach,” said 2008 Nobel laureate Francoise Barre-Sinoussi, co-discoverer of HIV as the cause of AIDS, and the group’s leader. “We are very optimistic that a functional cure is possible.”

More than 5,500 scientists are attending the conference, which ends Wednesday. To access the Rome Statement, visit http://www.iasociety.org/Default.aspx?pageId=583.

Male Circumcision Boosts Sexual Pleasure, AIDS Forum Told
Agence France Presse, (07.20.2011)
Efforts to prevent HIV infection by promoting male circumcision — which reduces the risk of female-to-male transmission by about 60 percent — got a boost from news presented Wednesday at the 6th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention in Rome.

In a study of 316 men, average age 22, circumcised between February and September 2009, 82.3 percent said they were “very satisfied” with the operation a month later, and 17.7 percent rated themselves “satisfied,” reported researchers from Uganda’s University of Makerere.

In addition, 87.7 percent found it easier to reach orgasm after the procedure, and 92.3 percent said they achieved more sexual pleasure. More than 95.4 percent said their partner was satisfied with the look of their circumcised penis, a sentiment shared by nine-tenths of the men. One year after the operation, one-quarter of the 220 then-sexually active men said they used condoms.

Although male circumcision does not directly reduce a female's risk of acquiring HIV from an infected partner, it confers an indirect, statistical advantage to women by reducing the number of infected men.

As of mid-2010, about 175,000 medical circumcisions had been performed to help prevent HIV in 13 high-prevalence countries, UNAIDS said.

Global Polio Eradication Efforts Unlikely To Meet 2012 Goal, Health Experts Say
An independent group of health experts, formed last year at the request of the WHO, on Wednesday warned that the world is not on track to eradicate polio by the end of 2012, the Associated Press reports. The group "said in a new report released Wednesday that it was 'unshakable' in its view that the global effort to stop polio by the end of next year is at risk. Two previous eradication targets have already been missed and the effort costs about $1 billion every year," the news service writes. "Unless some hard messages are given with no holds barred, progress will not be made," said Sir Liam Donaldson, the group's chair. Eradication is still possible, but major changes are needed, he said, according to the news agency (7/20).

In related news, UNICEF on Tuesday said several new polio cases in Northern Nigeria are threatening to erase efforts to eradicate the disease in that country, Agence France-Presse reports. "Polio cases in Nigeria dropped to 21 in 2010 from a staggering 338 cases in 2009," AFP notes. However, according to Jacques Boyer, deputy head of UNICEF in Nigeria, 20 cases of polio have been reported in six northern states this year (7/19).

WHO Denounces TB Blood Tests In First-Ever 'Negative' Policy Recommendation
The WHO "called on Wednesday for an immediate halt to the use of blood tests to detect active tuberculosis [TB], saying they were faulty and leave millions of people at risk," Reuters reports. The agency had never recommended the tests, which are manufactured in Europe and North America and "are often targeted at countries with weak regulatory mechanisms for diagnostics, where questionable marketing incentives can override the interests of patients," WHO TB specialist Karin Weyer said during a press conference to announce the policy recommendation, according to Reuters (Evans, 7/20).
The move represents the first time the WHO has issued an "explicit 'negative' policy recommendation against a practice that is widely used in tuberculosis care. It underscores the Organization's determination to translate strong evidence into clear policy advice to governments," according to a WHO press release (7/20).

**Battle of the bugs**

**Pseudomonas deploys a toxin delivery machine to breach cell walls of rivals without hurting itself**

Microbiologists have uncovered a sneaky trick by the bacterium *Pseudomonas aeruginosa* to oust rivals. It deploys a toxin delivery machine to breach cell walls of competitors without hurting itself.

Its means of attack helps it survive in the outside environment and may even help it cause infection. *P. aeruginosa* is a common bacterium that lives in soil, and also an opportunistic pathogen best known for infecting the lungs of cystic fibrosis patients.

The scientists discovered that *P. aeruginosa* injects toxins into rival bacteria with a needle-like puncturing device called the type VI secretion system (T6SS). The toxins degrade competitors’ protective barricades – their cell walls. The research report also delineates the complex defensive mechanisms by which *P. aeruginosa* protects itself from its own artillery.

The journal *Nature* will publish the findings July 21.

While generally harmless to healthy people, this versatile bacterium takes advantage of those with weakened immune defenses, explained lead author Alistair Russell, a National Science Foundation fellow in the laboratory of Joseph Mougous, assistant professor of microbiology at the University of Washington (UW) and the study's senior author.

*P. aeruginosa*'s ability to thrive in the thick airway mucous of cystic fibrosis patients and in burned or otherwise severely damaged skin makes it a major public health concern. All of these environments have one thing in common: other bacteria.

According to Russell, "Competition among bacteria is brutal and fierce." By killing off competitors, *P. aeruginosa* widens its territory, leading to its overall success. Moreover, the better able it is to outlast other bacteria in the environment, the better chance it has of coming in contact with, and colonizing, people.

"*Pseudomonas* is never going to encounter an infection site if it can’t survive in the outside world," Russell added.

The researchers have detailed the mechanism of the T6SS, which breaches a protective layer present in bacteria and delivers toxic proteins that degrade the cell wall. After the cell wall is compromised, the cell bursts like an overfilled water balloon.

The T6SS mechanism transports toxins so that they never enter *P. aeruginosa*'s cell wall space. To thwart an attack from other members of its species, each *P. aeruginosa* cell also has specific immunity proteins that inactivate toxins injected by neighboring cells.

Bacterial species that lack these immunity proteins are susceptible.

The study also confirms previous observations of the evolutionary similarity between the T6SS needlelike delivery mechanism and bacteriophage – viruses that infect bacteria.

Interestingly, in a technique called "phage therapy," scientists have long sought to exploit the antibacterial properties of these viruses in order to treat bacterial infections.

One limitation is that bacteriophage are relatively unstable and require a host bacterium to increase their numbers. Mougous and his colleagues are excited by the potential of the antibacterial properties of the T6SS to be used in an analogous way.

Russell explained, "We might be able to take helpful bacteria, give them this system genetically, and increase their ability to clear out professional pathogens – those bacteria that make their living causing disease."

Knowledge of this complex bacterial antimicrobial mechanism also might help in the design of more sophisticated drugs.

"If scientists could inhibit this secretion system in *Pseudomonas* through a new type of antibiotic, this opportunistic pathogen would not be able to break through the normal, healthy barrier of bacteria in the human body," Russell said.
Newly Designed Molecule Blocks Chlamydia Bacteria

ScienceDaily (July 20, 2011) — Researchers at Duke University Medical Center have discovered a way to block the damaging actions of Chlamydia, the bacteria responsible for the largest number of sexually transmitted infections in the United States.

The team, which included Duke University microbiologists and chemists, designed a molecule that takes away the bacteria’s self-defense mechanisms.

The therapies that could come from this discovery mark a new type of antimicrobial approach. Instead of directly killing the bacteria, they will disarm a central weapon of Chlamydia, and let the body take care of the rest.

Chlamydia infections are symptomless at the beginning, but can become chronic in women and lead to pelvic inflammatory disease and infertility as it infects cells in the uterus and fallopian tubes. It’s generally harmless to men. While these infections can be treated with antibiotics, Chlamydia can be easily reacquired and arise as a greater problem again. There are more than nearly 3 million new cases in the U.S. each year.

A virulence factor that Chlamydia produces, called CPAF, emerged as a promising target to shut down because it plays an important role in protecting the bacteria within hiding places (vacuoles) in human cells. CPAF also prevents the human cell from committing suicide when it senses that it has been invaded by a pathogen (a common self-defense mechanism), giving Chlamydia bacteria an extended chance to multiply and stay hidden.

The study was the cover story in the July 21 print edition of Cell Host and Microbe.

Microbiologists and genetics experts led by Raphael Valdivia, Ph.D., an associate professor in the Duke Department of Molecular Genetics and Microbiology, completed the work that narrowed down the search to an enzyme that Chlamydia produces, a protease called CPAF.

"Chlamydia makes this master protease that takes over the whole cell and prevents it from mounting an effective, pathogen-killing immune response," Valdivia said. "Chlamydia is unique among pathogens, in that it can co-exist within humans without causing symptoms for a long time. This reflects a careful balance between the host and the pathogen. We think CPAF is central to this balance. Therefore, if we disarm it, we can tilt the equation toward the human host and mount an effective immune response that will not only clear the infection but prevent it from re-emerging."

The Duke chemists, led by Dewey McCafferty, Ph.D., a professor in the Duke Departments of Chemistry and Biochemistry, designed a molecule that could block the CPAF activity inside of human cells.

"Typically, to design a potent, specific, and cell-permeable inhibitor is a complicated undertaking and inhibitor designs don’t work right away," McCafferty said. "But in this case, it worked on the first try. Professor Valdivia’s group of microbiologists and my group of chemical biologists worked to establish which qualities we needed to incorporate into a CPAF inhibitor. The results are very exciting, because we have an inhibitor lead molecule that may form the basis for a new class of anti-Chlamydial drugs."

They found that when CPAF was blocked over time by their designed molecule, the protective home that the bacteria make for themselves within the infected cells degraded, and CPAF no longer could degrade the proteins in the cell that would normally mount an immune response to the infection.

When CPAF is inhibited, the infected human cells effectively "commit suicide," Valdivia said. "When the infected human cell dies, so does Chlamydia, and this ends the infection."

Valdivia said that the findings could yield new therapeutic approaches that might turn a natural infection into a vaccination.

"By stopping the cloaking response of the bacteria, we are essentially revealing where they are in the cell and allowing our own immune system to take over and destroy the pathogens," McCafferty said.

Journal Reference:

Virginia Lags US in Girls with HPV Vaccine

Richmond Times-Dispatch, (07.04.2011) Tammie Smith

Federal immunization data show roughly 37 percent of Virginia girls ages 13-17 had at least one dose of human papillomavirus (HPV) vaccine in 2009 — below the national average of 44 percent.

The lower rate of vaccine uptake comes despite a 2008 state law mandating that sixth-grade girls receive the first of three HPV vaccine doses. Parents, however, are allowed to opt their daughter out of the
vaccination requirement. Massachusetts had the highest rate of 69 percent, followed by Rhode Island at 68 percent. Mississippi had the lowest rate, 23 percent.

HPV is the primary cause of cervical cancer, genital warts and other conditions. Since the virus is sexually transmitted, the vaccine is most effective when administered prior to the start of sexual activity. Sandra Sommer of the state Department of Health’s immunization division said educational materials on HPV vaccination are provided to schools for parents of rising sixth-grade girls. The information is available online at http://www.vdh.virginia.gov/epidemiology-immunization/documents/SchoolRegulations/HPVLetterEdncFlyerApril.pdf.

Hormonal contraceptive use increases women’s risk of acquiring and transmitting HIV
Roger Pebody
Published: 21 July 2011
A two-year, seven-country study has concluded that women using hormonal contraceptives, particularly injectable forms, are at a greater risk both of acquiring HIV themselves and of passing it on to a male sexual partner. Presenting the results to the International AIDS Society conference in Rome yesterday, Renee Heffron of the University of Washington said that strategies are needed to improve access to and uptake of lower-dose contraceptives and non-hormonal methods – such as IUDs, implants, patches or combination injectables.

The new study will be considered alongside the findings of a number of other studies that have also found an association between hormonal contraceptive use and HIV infection in women. However, this link has not been found consistently in all research. Most notably, a five-year study conducted with 6109 women in Zimbabwe, Uganda and Thailand found that neither the combined oral contraceptive pill nor DMPA (Depo-Provera) injections were associated with HIV infection.

The new findings are also notable for their investigation of the effect of contraceptive use on onward transmission to men – a previously unexplored area.

The data come from an analysis of 3790 serodiscordant couples (i.e. 7580 people) in South Africa, Botswana, Zambia, Tanzania, Uganda, Kenya and Rwanda. In two-thirds of the couples, the female partner was HIV-positive, in one-third, the man.

The couples were recruited either as part of the Partners in Prevention cohort or for the Couples Observational Study (a study of immune correlates of HIV protection). Every three months, data were recorded on contraceptive use and sexual behaviour. HIV-negative partners were tested for HIV at the same frequency; only seroconversions that were determined by gene sequencing to have been acquired from the study partner were included in the analysis.

Most couples were married and had at least one child together, on average. At enrolment around a quarter of couples reported having unprotected sex in the last month. A quarter of couples experienced a pregnancy during the two-year study.

HIV acquisition in women
Overall, 21% of HIV-negative women used hormonal contraception at least once during the study period. Injectable contraception was used at least once by 16% of women and oral contraception was used at least once by 7% of women.

Of the 1314 HIV-negative women, 73 acquired HIV. Incidence among women using contraception was 6.61 per 100 person-years, compared to 3.78 per 100 person-years among women not using contraception.

After adjusting for confounding factors in multivariate analysis, women using any hormonal method had twice the risk of acquiring HIV as other women (hazard ratio 1.98, 95% confidence interval 1.06 – 3.68).

An analysis of women using injectable methods gave similar results. However, the findings were not statistically significant for women using oral contraceptives – this may be because fewer women in the study used oral methods, so there was not statistical power.

HIV transmission to men
Of the HIV-negative men, one-third of their female partners used hormonal contraception at least once during the study. Injectable contraception was used by 27% and oral contraception by 9%.

Of the 2476 men, 59 acquired HIV from their primary partner during the study. HIV incidence in the partners of hormonal contraceptive users was 2.61 per 100 person-years, compared to 1.51 per 100 person-years among men whose partners did not use contraception.

After statistical adjustment, men whose partners used any form of hormonal contraceptive had twice the risk of acquiring HIV as other men (hazard ratio 1.97, 95% confidence interval 1.12 – 3.45).
Again, the findings in relation to injectables were very similar, whereas those in relation to oral contraceptives were not statistically significant.

A possible mechanism for the increased transmission from women to men is that users of hormonal contraceptives had higher levels of genital HIV viral load than other women.

An examination of genital samples from 1691 women – with the figures adjusted for blood viral load and CD4 count – found that women using hormonal contraception were more likely to have detectable genital viral loads and a greater quantity – by 0.14 logs. The difference was driven by injectable users who had a 67% increased odds of having a detectable genital viral load compared to non-users.

**Implications**

“It’s clear that the benefits of effective hormonal contraception are unequivocal – especially when you think about maternal mortality – and the risk of HIV infection really needs to be balanced with these benefits,” researcher Renee Heffron said.

She recommended that women and couples should be counselled about both the HIV risks and the importance of dual contraception – condom use in conjunction with hormonal contraceptive use.

Ward Cates of Family Health International and Professor Helen Rees of the Wits Reproductive Health and HIV Institute both commented that the findings underline the relevance of the intrauterine device (IUD) as a contraceptive choice for women in high-prevalence settings.

Rees noted that the South African policy on contraception was in the process of being revised and would take these findings into account. "The entire policy is being written in the context of HIV, because there is no such thing as a pocket of HIV in our setting," she said.

She noted that, while current thinking was that lower-dose hormonal methods would be safer, this has not actually been empirically tested. She called for randomised controlled trials, which would not be subject to the challenges of bias and confounding factors found in all observational studies (including the one described here).

She also commented that establishing the safety of hormonal methods is particularly important in the light of moves to develop multipurpose health technologies – such as microbicides and vaginal rings – which could simultaneously prevent unwanted pregnancy, HIV infection and other sexually transmitted infections.

**Reference**


**Skin sentry cells promote distinct immune responses**

A new study reveals that just as different soldiers in the field have different jobs, subsets of a type of immune cell that polices the barriers of the body can promote unique and opposite immune responses against the same type of infection. The research, published online on July 21st by Cell Press in the journal *Immunity,* enhances our understanding of the early stages of the immune response and may have important implications for vaccinations and treatment of autoimmune diseases.

Dendritic cells serve as sentries of the immune system and are stationed at the body's "outposts," like the skin, where they are likely to encounter invading pathogens. When dendritic cells encounter pathogen-associated antigens (molecules that trigger an immune response), they process the antigen and present it to other responding immune cells in an effort to initiate a cellular cascade resulting in clearance of the pathogen. This is a critical part of the immune response because many responding immune cells cannot "see" antigen and initiate the proper protective response unless the antigen is properly presented by a dendritic cell.

"There are at least three different types of dendritic cells in the skin," explains senior study author, Dr. Daniel Kaplan from the University of Minnesota. "Despite studies examining these cells, the basic question of whether skin resident dendritic cells have unique or redundant functions remains unresolved." Dr. Kaplan and colleagues developed a model of yeast infection that is limited to the superficial layer of the skin and studied antigen-specific immune responses in mice lacking specific subsets of skin dendritic cells.

The researchers discovered that direct presentation of antigen by one type of dendritic cell, Langerhans cells, was necessary and sufficient for the generation of antigen-specific T helper-17 (Th17) cells but not the generation of cytotoxic lymphocytes (CTL). T helper cells play a key role in orchestrating the immune response, whereas CTLs can directly destroy infected cells. While Th17 cells play productive roles in indirectly eliminating pathogens when their response is dysregulated, they have been implicated...
in autoimmune disease. Meanwhile, another subset of dendritic cells was required for the generation of antigen-specific CTLs and inhibited the ability of other dendritic cells to promote Th17 cell responses. "Our work demonstrates that dendritic cells in the skin promote distinct and opposing antigen-specific responses," concludes Dr. Kaplan. "This has important implications for vaccination strategies that selectively target dendritic cell populations. In addition, the requirement for Langerhans cells in the development of Th17 cells suggests these cells may participate in the early pathogenesis of Th17 cell-mediated skin diseases such as psoriasis."

**UNC researchers identify seventh and eighth bases of DNA *****

(Embargoed) CHAPEL HILL – For decades, scientists have known that DNA consists of four basic units—adenine, guanine, thymine and cytosine. Those four bases have been taught in science textbooks and have formed the basis of the growing knowledge regarding how genes code for life. Yet in recent history, scientists have expanded that list from four to six.

Now, with a finding published online in the July 21, 2011, issue of the journal *Science*, researchers from the UNC School of Medicine have discovered the seventh and eighth bases of DNA.

These last two bases—called 5-formylcytosine and 5-carboxylcytosine—are actually versions of cytosine that have been modified by Tet proteins, molecular entities thought to play a role in DNA demethylation and stem cell reprogramming.

Thus, the discovery could advance stem cell research by giving a glimpse into the DNA changes—such as the removal of chemical groups through demethylation—that could reprogram adult cells to make them act like stem cells.

"Before we can grasp the magnitude of this discovery, we have to figure out the function of these new bases," said senior study author Yi Zhang, Ph.D., Kenan Distinguished Professor of biochemistry and biophysics at UNC and an Investigator of the Howard Hughes Medical Institute. "Because these bases represent an intermediate state in the demethylation process, they could be important for cell fate reprogramming and cancer, both of which involve DNA demethylation."

Much is known about the "fifth base," 5-methylcytosine, which arises when a chemical tag or methyl group is tacked onto a cytosine. This methylation is associated with gene silencing, as it causes the DNA's double helix to fold even tighter upon itself.

Last year, Zhang's group reported that Tet proteins can convert 5 methylC (the fifth base) to 5-hydroxymethylC (the sixth base) in the first of a four step reaction leading back to bare-boned cytosine. But try as they might, the researchers could not continue the reaction on to the seventh and eighth bases, called 5 formylC and 5 carboxyC.

The problem, they eventually found, was not that Tet wasn't taking that second and third step, it was that their experimental assay wasn't sensitive enough to detect it. Once they realized the limitations of the assay, they redesigned it and were in fact able to detect the two newest bases of DNA. The researchers then examined embryonic stem cells as well as mouse organs and found that both bases can be detected in genomic DNA.

The finding could have important implications for stem cell research, as it could provide researchers with new tools to erase previous methylation patterns to reprogram adult cells.

It could also inform cancer research, as it could give scientists the opportunity to reactivate tumor suppressor genes that had been silenced by DNA methylation.

**Hepatitis C is transmitted by unprotected sex between HIV-infected men**

**Ongoing epidemic in New York City in HIV-infected men**

Sexual transmission of hepatitis C virus (HCV) is considered rare. But a new study by researchers at Mount Sinai School of Medicine, working with the Centers for Disease Control and Prevention (CDC), provides substantial evidence that men with HIV who have sex with other men (MSM) are at increased risk for contracting HCV through sex.

The results of the study are published in today's edition of the CDC's Morbidity and Mortality Weekly Report.

HCV transmission primarily occurs through exposure to blood, and persons who inject drugs at greatest risk. But when Mount Sinai researchers observed a large increase in the number of new cases of HCV transmission among HIV-infected men who did not inject drugs, they took a closer look to examine the role of sexual transmission among these men.
The researchers identified 74 HIV-infected men between October 2005 and December 2010 who had documented new HCV infection and yet reported no other risk factor for HCV infection, including injection drug use. When they compared 22 of these men with a control group of 53 closely matched HIV-infected MSM who did not have HCV infection, they found that the men who had recently contracted HCV were 23 times more likely to have had unprotected anal sex with men. In addition, HCV genetic analysis suggested that HCV was transmitted within social networks of these men, consistent with the presence of a city-wide epidemic.

"While hepatitis C is rarely transmitted among stable heterosexual couples, this is clearly not the case among HIV-infected MSM in New York City," said Dr. Daniel Fierer, Assistant Professor of Medicine and Infectious Diseases at Mount Sinai School of Medicine. "MSM, and to some extent their health care providers are generally not aware that having unprotected receptive sex can result in HCV infection. The good news is that the cure rate for new HCV infections is very high with early treatment, but without regular testing of the men at risk, these largely asymptomatic infections may be missed and this opportunity lost."

"Our study suggests that HIV-infected MSM should take steps to protect themselves and others by using condoms. Also, health care providers should be screening these men for hepatitis C, and public education and outreach programs should include information about these risks," Dr. Fierer concluded.

**Hospital bacteria outbreak linked to nasal spray**
Chicago, IL—Infection control researchers investigating a rare bacterial outbreak of *Burholderia cepacia* complex (Bcc) identified contaminated nasal spray as the root cause of the infections, leading to a national recall of the product. An article in the August issue of *Infection Control and Hospital Epidemiology*, the journal of the Society for Healthcare Epidemiology of America (SHEA), describes how researchers were able to trace the outbreak back to the nasal decongestant spray.

Bcc is a group of Gram-negative bacteria that can cause hard-to-treat infections. Patients with underlying medical conditions such as lung disease and weakened immune systems are at greater risk of contracting Bcc. When patients in a Denver children’s hospital began testing positive for the bacteria in 2003, investigators suspected that a batch of Major Twice-a-Day Nasal Spray, a brand that each of the patients had used, might be to blame. However, standard tests of the spray did not find any bacteria initially.

Noticing some peculiarities in the initial tests, the investigators decided to retest the spray using a non-standard culture medium. The second set of tests was positive for Bcc, the same strain as was identified in patients. The nasal spray contained a preservative agent that can interfere with standard bacterial cultures and the second set of tests neutralized the preservative, allowing the detection of the bacteria.

The spray was voluntarily recalled by the manufacturer, but the findings raise lingering questions about how manufacturers should test nasal spray products before distribution. "If standard culturing methods were used by the manufacturer then they may not have [discovered] this organism," the researchers write.

"Nasal spray products are among the most widely used over-the-counter pharmaceuticals, but to date they are not required by the FDA to be sterile," said Susan Dolan, one of the article’s authors. "Given the implications of Bcc infections we question this decision."

Other products, such as mouthwash, nebulization therapy, tap water, disinfectants, and reusable temperature probes have previously been implicated as Bcc outbreak sources.


**1 in 4 gay/lesbian high school students are homeless**
Among homeless teens, GLB teens are more likely to live away from their families
Roughly 1 in 4 lesbian or gay teens and 15 percent of bisexual teens are homeless, versus 3 percent of exclusively heterosexual teens, finds a Children’s Hospital Boston study of more than 6,300 Massachusetts public high school students. Moreover, among teens who were homeless, those who were gay, lesbian or bisexual (GLB) were consistently more likely than heterosexuals to be on their own, unaccompanied by a parent or guardian.

The study, published online July 21 by the *American Journal of Public Health*, is the first to quantify the risk of homelessness among teens of different sexual orientations with population-based data. "Prior
studies in homeless street youth have found that sexual minorities occur in much higher numbers than we'd expect based on their numbers in the community in general," says Heather Corliss, PhD, MPH, of the Division of Adolescent and Young Adult Medicine at Children's, the study's first author. "This study looked at the magnitude of the difference for the first time."

Corliss and colleagues analyzed data from the 2005 and 2007 Massachusetts Youth Risk Behavior Surveys (YRBS). The YRBS, conducted every other year in most U.S. states, draws a representative sample of students in grades 9 through 12. In 2005, Massachusetts was the first state to add a multiple-choice question assessing homeless status, asking "What is your primary nighttime residence?" or "Where do you typically sleep at night?" Homelessness was defined as lacking a fixed, regular and adequate nighttime residence, as per the McKinney-Vento Homelessness Assistance Act, the primary federal legislation dealing with the education of homeless children and youth in U.S. public schools.

The initial sample of 6,653 students was narrowed to 6,317 who gave full information on their sexual orientation and homelessness status. Less than 5 percent of students overall identified themselves as GLB, yet they accounted for 19 percent of those who identified themselves as homeless.

Rates of homelessness were 3.2 percent among exclusively heterosexual students, 12.5 percent among heterosexuals reporting same-sex partners, 15 percent among bisexuals, 25 percent among lesbian/gay students, and 20 percent among students who said they were unsure of their sexual orientation.

Among the youth who were homeless, those who were not exclusively heterosexual were more likely to be living away from their families. Among boys identifying as gay, 15 percent were homeless but unaccompanied by parents/guardians, and 8 percent were homeless but living with parents. Among lesbian girls, 22.5 percent were homeless and unaccompanied, while just 3.8 percent were homeless but with their parents. The same pattern held among bisexual students, among heterosexuals with same-sex partners, and among males unsure of their sexual orientation.

"Teens with a sexual minority orientation are more likely than heterosexual teens to be unaccompanied and homeless rather than part of a homeless family," says Corliss. "This suggests that they may be more likely to be mistreated or rejected by their families and more likely to leave home."

The researchers hope their findings will raise awareness of the vulnerability of GLB youth to homelessness, particularly among school administrators and other professionals working with adolescents. Homeless people are well documented as being at increased risk for victimization, physical and sexual abuse, mental health problems, substance use problems and sexual risk behaviors. These risks are even greater for teens who lack their families' supervision and support.

"The high risk of homelessness among sexual minority teens is a serious problem requiring immediate attention," says Corliss. "These teens face enormous risks and all types of obstacles to succeeding in school and are in need of a great deal of assistance."

The study has limitations in being done only in Massachusetts, where attitudes toward homosexuality tend to be more favorable, so it possibly underestimates the proportion of GLB youth that are homeless nationally. It also included only students who were at school on the day the survey was administered, so may have missed more homeless youths, who are more likely to be absent from school. Finally, because it was based on the YRBS, it wasn't able to assess family relationships or whether teens were "out" about their sexuality.

Newly Designed Molecule Blocks Chlamydia Bacteria

ScienceDaily (July 20, 2011) — Researchers at Duke University Medical Center have discovered a way to block the damaging actions of Chlamydia, the bacteria responsible for the largest number of sexually transmitted infections in the United States.

The team, which included Duke University microbiologists and chemists, designed a molecule that takes away the bacteria's self-defense mechanisms. The therapies that could come from this discovery mark a new type of antimicrobial approach. Instead of directly killing the bacteria, they will disarm a central weapon of Chlamydia, and let the body take care of the rest.

Chlamydia infections are symptomless at the beginning, but can become chronic in women and lead to pelvic inflammatory disease and infertility as it infects cells in the uterus and fallopian tubes. It's generally harmless to men. While these infections can be treated with antibiotics, Chlamydia can be easily reacquired and arise as a greater problem again. There are more than nearly 3 million new cases in the U.S. each year.
A virulence factor that *Chlamydia* produces, called CPAF, emerged as a promising target to shut down because it plays an important role in protecting the bacteria within hiding places (vacuoles) in human cells. CPAF also prevents the human cell from committing suicide when it senses that it has been invaded by a pathogen (a common self-defense mechanism), giving *Chlamydia* bacteria an extended chance to multiply and stay hidden.

The study was the cover story in the July 21 print edition of *Cell Host and Microbe*.

Microbiologists and genetics experts led by Raphael Valdivia, Ph.D., an associate professor in the Duke Department of Molecular Genetics and Microbiology, completed the work that narrowed down the search to an enzyme that *Chlamydia* produces, a protease called CPAF.

"*Chlamydia* makes this master protease that takes over the whole cell and prevents it from mounting an effective, pathogen-killing immune response," Valdivia said. "*Chlamydia* is unique among pathogens, in that it can co-exist within humans without causing symptoms for a long time. This reflects a careful balance between the host and the pathogen. We think CPAF is central to this balance. Therefore, if we disarm it, we can tilt the equation toward the human host and mount an effective immune response that will not only clear the infection but prevent it from re-emerging."

The Duke chemists, led by Dewey McCafferty, Ph.D., a professor in the Duke Departments of Chemistry and Biochemistry, designed a molecule that could block the CPAF activity inside of human cells.

"Typically, to design a potent, specific, and cell-permeable inhibitor is a complicated undertaking and inhibitor designs don't work right away," McCafferty said. "But in this case, it worked on the first try. Professor Valdivia's group of microbiologists and my group of chemical biologists worked to establish which qualities we needed to incorporate into a CPAF inhibitor. The results are very exciting, because we have an inhibitor lead molecule that may form the basis for a new class of anti-Chlamydial drugs."

They found that when CPAF was blocked over time by their designed molecule, the protective home that the bacteria make for themselves within the infected cells degraded, and CPAF no longer could degrade the proteins in the cell that would normally mount an immune response to the infection.

When CPAF is inhibited, the infected human cells effectively "commit suicide," Valdivia said. "When the infected human cell dies, so does *Chlamydia*, and this ends the infection."

Valdivia said that the findings could yield new therapeutic approaches that might turn a natural infection into a vaccination.

"By stopping the cloaking response of the bacteria, we are essentially revealing where they are in the cell and allowing our own immune system to take over and destroy the pathogens," McCafferty said.

**Journal Reference:**


**IAS 2011: New NNRTI Lersivirine Looks Good in Phase 2 Study**

Published on Friday, 21 January 2011 00:00
Written by Liz Highleyman

Lersivirine, an investigational non-nucleoside reverse transcriptase inhibitor (NNRTI), lowered HIV viral load about as well as efavirenz (Sustiva) for people starting antiretroviral therapy for the first time, researchers reported at the 6th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2011) this week in Rome.

Lersivirine (formerly known as UK-453,061), being developed by ViiV Healthcare, has a unique binding pattern to HIV's reverse transcriptase enzyme, enabling it to remain active against HIV with certain NNRTI resistance mutations (including Y181C changes).

Anton Pozniak from Chelsea and Westminster Hospital in London reported findings from a Phase 2b trial (Study A5271015) comparing lersivirine vs efavirenz for first-line therapy.

This multinational study included 195 treatment-naive participants with no reverse transcriptase resistance mutations evident at baseline. About three-quarters were men, about 60% were white (though this varied across sites) and the average age was 36 years. The median baseline CD4 cell count was approximately 320 cells/mm³.

Participants were stratified according to viral load (above or below 10,000 copies/mL) and geographic region. About one-third lived in South Africa, with the rest in Europe, North and South America, and Australia; a corresponding proportion had HIV Clade C, whilst most of the rest had Clade B.
Participants were randomly assigned to received 500 mg lersivirine, 750 mg lersivirne, or placebo once-daily, in combination with tenofovir/emtricitabine (the drugs in Truvada).

Results

- In an overall intent-to-treat analysis at 48 weeks, 79% of participants in both lersivirine dose groups achieved viral load below 50 copies/mL, compared with 89% of those taking efavirenz, not a statistically significant difference.
- CD4 cell gains were good in all arms at about 100 cells/mm$^3$ per month.
- Both the 500 mg and 750 mg doses of lersivirine did not work as well as efavirenz for people with high viral load (75% vs 62% vs 82%, respectively).
- This was also the case among South Africans compared with patients in higher-income countries (72% vs 68% vs 83%, respectively).
- Further analysis found that the viral load difference was significant only among South Africans.
- 12 participants in each lersivirine arms and 9 in the efavirenz arm discontinued treatment early.
- Lersivirne was somewhat better tolerated than efavirenz overall.
- Serious adverse events and discontinuations for this reason were uncommon and frequency was similar across arms.
- People taking lersivirine experienced fewer neuropsychiatric side effects, as expected, but had more nausea (usually mild).
- Looking at the secondary endpoint of changes in blood lipids, participants taking lersivirine had:
  - smaller increases in total cholesterol;
  - smaller increases in triglycerides;
  - larger increase in HDL "good" cholesterol;
- However, the ratio of total-to-HDL cholesterol remained the same in all arms.
- Overall, Pozniak described lersivirine as "lipid neutral."
- Among participants who experienced virological failure, emergence of resistance mutations occurred more often in the 500 mg lersivirine arm than the higher-dose lersivirine or efavirenz groups.
- The K103N mutation was not seen in anyone taking lersivirine and one patient taking efavirenz.
- In discussing these findings, Pozniak explained that the apparently slightly worse virological suppression with lersivirine was driven by people with high viral load in South Africa, suggesting this may be attributable to poor adherence. Although lersivirine looks promising, he stressed that this analysis was not designed to determine superiority or non-inferiority, and Phase 3 studies are planned.

7/21/11

Reference


Bid to Put the Brakes on Disease in Africa

Business Day (Johannesburg), (07.14.2011)

HIV prevention activities along southern African transportation routes are getting a boost thanks to a five-year grant from the Global Fund to Fight AIDS, TB and Malaria.

North Star Alliance has signed an agreement with the Southern African Development Community (SADC) to deliver cross-border prevention services to at-risk communities. The partnership plans to roll out 29 mobile health clinics, which will offer basic health services, STD treatment, HIV counseling and testing, condom distribution and referrals to other facilities when needed.

“North Star is an international [nongovernmental organization] that uses best practices in supply chain management, innovations in network technology and inside knowledge of the transport industry to support a network of roadside wellness centers,” said Doreen Sanje, a technical adviser to SADC. “These provide basic health care, HIV- and [STD]-related prevention and treatment services and referrals to district and local health facilities for long-haul truck drivers, sex workers, mobile populations and communities.”

“An important service will be behaviors to implement change — communication strategies that will encourage and support people to adopt healthier lifestyles and safe-sex practices, such as consistent
condom use, knowing their HIV status and reducing the number of sexual partners,” said Michael Becker, general manager from North Star’s Durban office, who will run the project.

Statistical data on HIV and STD incidence will be gathered, and the project will track trends and emerging disease patterns across the region for research purposes. An encrypted system will allow patients to access their confidential records anywhere in the North Star network.

Benefitting countries include: Angola, Botswana, the Democratic Republic of Congo, Lesotho, Malawi, Mozambique, Namibia, South Africa, Swaziland, Tanzania, Zambia and Zimbabwe.

No hiding place
The long-sought goal of a cure for AIDS is inching closer
Jul 21st 2011 | from the print edition
AIDS researchers, many of whom have been meeting this week in Rome under the auspices of the International AIDS Society, are rightly pleased with the progress they have made. In particular, the use of antiretroviral drugs has not only revolutionised treatment of HIV infection, but also offers the prospect of stopping the spread of the virus. In a matter of weeks, these drugs reduce the number of viruses per millilitre of infected blood from millions to less than 50. That deals with both symptoms and infectivity. Unless a patient stops taking the drugs, or goes on to develop resistance to them, he can expect to live almost as long as an uninfected individual.

But good as they are at keeping viral levels low, antiretrovirals never destroy the virus completely and thus cure the patient once and for all. There are two reasons. One is that, although HIV reproduces mainly in immune-system cells called T-cells, it also lives in certain cells of the brain, gut and lymph nodes. In these cells it is protected from the drugs by mechanisms that are, as yet, not fully understood. The other is that even in T-cells it sometimes stops replicating and becomes dormant. Since antiretrovirals work by interfering with the process of replication, dormant viruses are immune to their effects. Take the drugs away, and when a dormant virus wakes up again it will rapidly reinfect the body it is in.

The search for a cure for AIDS, then, has led only to frustration. And calls by the conference’s organisers to renew that search might be regarded by old hands as little more than platitudes. But they are not, for there is a glimmer of hope on the horizon. To deal with dormant viruses several researchers are taking what sounds like a counterintuitive approach. They are trying to wake the viruses up and so boost, rather than reduce, the amount of active HIV in a patient’s body. Their reasoning is that the now-active viruses will either kill the cells they are in (and thus themselves) or encourage the immune system to attack those cells.

Wake-up call and the purging croton
One drug that promises to do this is interleukin-7. This substance, which is being tested in several clinical trials in America, occurs naturally in the body and in normal conditions encourages the proliferation of the T-cells that HIV invades. One of the causes of viral dormancy is that the T-cell the virus resides in is itself in a resting state. Such cells on sabbatical do not churn out many proteins of their own, so the virus cannot hijack the protein-manufacturing process—which is how it reproduces.

The idea is that a dose of interleukin-7 will nudge the T-cell—and therefore the virus—into wakefulness. And it seems to work. Robert Murphy of Northwestern University, in Illinois, who is leading one of the clinical trials, says blips of reawakened virus can indeed be seen in patients’ blood after a dose of interleukin-7. Whether subsequent treatment with antiretrovirals can then cleanse the immune system completely remains to be seen. But this is a promising start.

An alternative approach is to activate the virus directly, rather than activating the cell it is living in. This is a way of dealing with the second cause of HIV inactivation. The virus must copy its genes into the host cells’ chromosomes before these genes can be used. And sometimes, those genes become so tightly packed away within their host chromosome that they cannot be read by the cell’s DNA-transcription mechanism. To be activated they must be liberated from the chromosomal coils.

A group of agents called histone deacetylase inhibitors can help here, says Sharon Lewin, director of the infectious-diseases unit at Alfred Hospital in Melbourne, who is about to start a clinical trial of a histone-deacetylase inhibitor called SAHA. Histones are proteins that regulate DNA packing, and histone deacetylases are enzymes that control the way those proteins work. One of their effects is to keep HIV genes switched off. So inhibiting their activity should switch those genes back on.

Until now, SAHA has been tested only in cell cultures. These tests have found that it increases the expression of dormant HIV genes fivefold. Combining it with other agents, in particular one called prostratin, makes it even more effective—at least, in a Petri dish. Prostratin is thought to activate a protein...
that promotes replication of the virus. In a study led by David Schaffer and Adam Arkin of the University of California, Berkeley, around 80% of latent HIV became active in cell cultures treated with a combination of SAHA and prostratin. Preliminary research suggests that prostratin may also prevent copies of the purged virus which are circulating in the bloodstream from integrating themselves back into healthy immune cells.

More powerful variants of prostratin are now in the offing. In the past, the substance has been extracted directly from plants, and was available only in small quantities. In 2008, however, Paul Wender of Stanford University found a way of synthesising it from the oil of the purging croton plant, which is abundant, and he has gone on to create tweaked versions of the molecule that, he claims, are 1,000 times more potent than prostratin.

Although none of the studies published so far has managed to reactivate all of the dormant HIV in either a cell culture or a human being, they are still an encouraging step. And Dr Schaffer and Dr Arkin suspect that complete reactivation may not be necessary. If the new treatments miss latent copies of the virus that are hard to activate, then those copies may, in any case, pose less of a risk of reactivating and replicating naturally, because they are in a deeper state of dormancy.

Unfortunately, none of these drugs deals with the other part of the problem: the viruses in the brain, gut and lymph nodes. But many workers in the field think T-cell dormancy a more significant cause of relapse than HIV in such reservoir tissues. If it can be dealt with, that will be a huge step towards the ultimate desideratum of HIV research—a simple and effective cure.

House Committee Votes To Reinstate 'Global Gag Rule'
The House Foreign Affairs Committee on Thursday voted to "reinstate a ban on providing foreign aid to groups that perform abortions or provide advice about the procedure," The Hill's "HealthWatch" blog reports on the "so-called 'global gag rule'" (Baker, 7/21).

The committee voted down an amendment to the draft FY12 Foreign Relations Authorization Act (HR 2583) presented by Rep. Howard Berman (D-Calif.), the committee's ranking Democrat, that would have stripped the language reinstating and expanding the "ban on funding international non-governmental organizations that discuss abortion known as the Mexico City Policy," according to Foreign Policy's "The Cable" blog. The language would expand the ban as "it would ban all funding for organizations that discuss abortion and not make exceptions for certain programs such as HIV/AIDS funding," the blog writes (Rogin, 7/21).

The committee also "blocked an amendment ... that would have banned any assistance to Pakistan in the wake of the raid that killed Osama bin Laden near the country's main military academy," Agence France-Presse reports (Tandon, 7/21).

The Malaria Policy Center's blog notes the passage of a bipartisan amendment to the authorization bill that "recognizes the tremendous burden malaria places on the world" and "the successful progress that has been made in the fight against malaria through both national and international efforts to prevent and treat malaria" (Todd, 7/21).

The committee passed the amended authorization act on a vote of 20-23, according to a committee statement (7/21).

Al-Shabab Says Ban On Aid Groups In Somalia Remains In Place; WFP Announces Resumption Of Airlifts
Two weeks after lifting a ban on certain aid groups providing assistance in Somalia, the militant Islamist group al-Shabab has announced that the ban remains in place" and said that the U.N.'s declaration of famine in two regions of the country was being used as "propaganda," Al Jazeera reports (7/22).

The announcement followed a statement by the World Food Program (WFP), one of the agencies banned by al-Shabab, that it plans to begin airlifting aid to the country "within days," aiming "to reach as many as 2.2 million Somalis," Bloomberg News writes (Varner, 7/21). "We are testing the ground to see how we can best get life-saving supplies in as quickly as possible to those at the epicentre of the famine in the south," WFP Executive Director Josette Sheeran said in a statement on Thursday (7/21).

Also on Thursday, the U.N. Food and Agriculture Organization announced an emergency meeting to be held on July 25 in Rome, which is expected to be attended "by ministers and senior representatives from its 191 member countries, other U.N. bodies, NGOs and regional development banks," Reuters notes. "The meeting was called at the request of France, current president of the Group of 20 leading
economies," according to the news agency (7/21). Attendees plan to discuss "how to deliver aid safely and effectively into Somalia," the Guardian notes (Rice, 7/21).

**Infanticide And Attempted Infanticide Common Crimes Among Inmates In Malian Capital's Women's Prison**

"Infanticide or attempted infanticide has become the most common crime after theft and assault among inmates at the prison for women and girls" in Mali’s capital city Bamako, the Associated Press/San Francisco Chronicle reports.

In Mali, "one of the poorest countries in the world, abortion is illegal and UNICEF estimates only eight percent of Malian women use contraception," the news agency notes. The article examines how "Muso Danbe, an organization that supports women and girls working as domestic workers," and education programs at the prison are assisting affected women gain employment after having babies or upon their release from prison (Vogl, 7/22).

**China's New Leadership Should End One-Child Policy**

"Chinese officials are fiercely attached to the one-child policy. They attribute to it almost every drop in fertility and every averted birth: some 400m more people, they claim, would have been born without it," an Economist editorial states, adding, "This is patent nonsense. Chinese fertility was falling for decades before the one-child policy took effect in 1979."

"The old leadership is wedded to the one-child policy, but the new leadership, which is due to take over next year, can think afresh. It should end this abomination as soon as it takes power," the Economist writes (7/21).

Friday, July 22, 2011

**A*STAR Scientist Discover How to Combat Hospital-Acquired Infections, Deadly Food Poisoning And Bioterrorism Toxins**

This study paves the way for developing toxin antidotes to safeguard public health and national security.

1. A team of scientists from A*STAR's Institute of Molecular and Cell Biology (IMCB) has discovered the secret recipe for 'antidotes' that could neutralize the deadly plant toxin Ricin, widely feared for its bioterrorism potential, as well as the Pseudomonas exotoxin (PE) responsible for the tens of thousands of hospital-acquired infections in immune-compromised patients all over the world. The results of this first ever genome-wide study to understand how the Ricin and PE toxins attack cells may also be useful for designing more effective antidotes against Diphtheria and Shiga-like toxins secreted by infectious strains of E. coli bacteria, such as those responsible for the recent food poisoning outbreak in Germany.

2. In this study, the team led by IMCB Principal Investigator, Dr Frédéric Bard examined the entire human genome of about 22,000 genes to identify those genes of normal host cell processes which Ricin and PE toxins hijack in order to kill the cell. Of the several host genes identified, the team discovered one called ERGIC2 to be an attractive therapeutic target because it is not only highly essential for Ricin but also required for PE intoxication. "This means that we could potentially develop a generic antidote that is effective against the two different types of toxins by blocking ERGIC2 function," said Dr Bard.

3. Ricin is an extremely potent poison that can easily be purified from the widely available castor beans. Security experts say an amount roughly equivalent to half a grain of rice is enough to kill an adult, making it 1,000 times more poisonous than cyanide. There are currently no known antidotes for Ricin, and the ease of production of this tasteless, odorless plant toxin is why ricin is feared for its immense bioterrorism potential.

4. Hospital-acquired infections (HAIs) are a major healthcare problem affecting millions of people around the world. The U.S. Centers for Disease Control and Prevention estimates that HAIs leads to US$45 billion in healthcare cost annually and results in nearly 100,000 deaths per year, making HAIs the fourth leading cause of death. The bacteria Pseudomonas aeruginosa that secretes PE toxin is a common cause of HAIs in vulnerable individuals, including those with burn injuries or receiving intensive care. Unfortunately, HAIs are increasingly difficult to treat because the emergence of antibiotic-resistant bacteria is on the rise. Similarly, the E. coli strain that produces Shiga toxins, found in the recent deadly food poisoning cases in Germany, were also resistant to
antibiotics. Moreover, in food poisoning cases caused by such toxin-producing bacteria, doctors refrain from using antibiotics as killing the bacteria actually causes more toxins to be released, bringing on the worst symptoms of the illness. There is therefore a real need worldwide for antidotes against these life-endangering toxins.

5. Highlighting the significance of this study, Dr Bard added, “Through this genome-wide screen, our understanding of how toxins interact with human cells at the molecular level expanded tremendously. Our hope is that with these new therapeutic targets identified from the human genome, we will be one step closer to finding toxin antidotes that will make hospital-acquired infections and enterotoxic E. Coli outbreaks a thing of the past.”

More about protein toxins

6. Though immunologically different from each other, Ricin, PE, Diphtheria and Shiga toxins all kill by destroying the cell’s protein synthesis ‘factories’, the place where all proteins necessary for the cell’s survival are produced. To travel to these protein ‘factories’ in the cell, the toxins first trick the host cell into turning off a natural defense mechanism that destroys foreign proteins. Next, they exploit the host cell’s internal transport pathway to reach the protein ‘factories’, destroying them and killing the cell. When this happens, cell death is imminent. If not contained, toxins released from dead cells can spread to neighboring healthy cells, resulting in rapid and widespread tissue and organ damage.

7. By identifying the specific host genes required for these toxins to attack the cell’s protein ‘factories’, this study effectively singled out the attractive therapeutic targets from the entire human genome for developing antidotes that could potentially be effective against any toxins that share the same mode of action. For instance, ERGIC2 was found to be an important component of the cell’s internal transport pathway that the toxins hijack to reach the cell’s protein ‘factories’.

Notes for Editor:
The research findings described in this news release can be found in the 21 July 2011 advance online issue of Developmental Cell under the title, "Genome-wide RNAi screens identify genes required for Ricin and PE intoxications" by Dimitri Moreau, Pankaj Kumar, Shyi Chyi Wang, Alexandre Chaumet, Shin Yi Chew, Hélène Chevalley and Frédéric Bard.

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Synopsis

Understanding the Cholera Epidemic, Haiti (very long)

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Abstract

After onset of a cholera epidemic in Haiti in mid-October 2010, a team of researchers from France and Haiti implemented field investigations and built a database of daily cases to facilitate identification of communes most affected. Several models were used to identify spatiotemporal clusters, assess relative risk associated with the epidemic’s spread, and investigate causes of its rapid expansion in Artibonite Department. Spatiotemporal analyses highlighted 5 significant clusters (p<0.001): 1 near Mirebalais (October 16–19) next to a United Nations camp with deficient sanitation, 1 along the Artibonite River (October 20–28), and 3 caused by the centrifugal epidemic spread during November. The regression model indicated that cholera more severely affected communes in the coastal plain (risk ratio 4.91) along the Artibonite River downstream of Mirebalais (risk ratio 4.60). Our findings strongly suggest that contamination of the Artibonite and 1 of its tributaries downstream from a military camp triggered the epidemic.

On October 21, 2010, the Haitian Ministry of Public Health and Population (MSPP) reported a cholera epidemic caused by Vibrio cholerae O1, serotype Ogawa, biotype El Tor (1). This epidemic was surprising as no cholera outbreak had been reported in Haiti for more than a century (1,2). Numerous media rapidly related the epidemic to the deadly earthquake that Haiti had experienced 9 months earlier. However, simultaneously, a rumor held recently incoming Nepalese soldiers responsible for importing cholera, along with accusations of illegal dumping of waste tank contents (3). A cholera outbreak was indeed reported in Nepal’s capital city of Kathmandu on September 23, 2010, shortly before troops left for Haiti (4,5). Two hypotheses then emerged to explain cholera in Haiti.
Some researchers posited the transmission of an environmental strain to humans \(^6\). Reasoning by analogy with cholera epidemiology in South Asia, they hypothesized that weather conditions, i.e., the La Niña phenomenon, might have promoted the growth of \(V.\) \textit{cholerae} in its environmental reservoir \(^6\). The second hypothesis suggested importation of the disease from a cholera-endemic country. The sequencing of 2 isolates of \(V.\) \textit{cholerae} supported this second hypothesis by establishing an exogenous origin, probably from southern Asia or eastern Africa \(^2\). Responding to a request from Haitian authorities to the French Embassy for the support of epidemiologists, we conducted a joint French–Haitian investigation during November 7–November 27, 2010, to clarify the source of the epidemic and its unusual dynamic.

**Morbidity and Mortality Survey**

As soon as the epidemic was recognized, a nationwide monitoring program was implemented to register all ambulatory patients, hospital admissions, and deaths \(^1\). Each day, all government and nongovernmental health facilities in Haiti reported cases to the Direction of Health in each department, which colligated data before sending them to MSPP. For this study, the departments were asked to provide more precise data corresponding to the 140 Haitian communes from October 16 through November 30. Probable cholera cases were defined as profuse, acute watery diarrhea in persons. In each department, bacteriologic confirmation was obtained only for the first cases. Children <5 years of age were included because age was not always reported. Community deaths were additionally reported by local authorities. Comparison with epidemiologic surveys performed by other actors (Doctors without Borders, medical brigades from Cuba) enabled confirmation of the consistency of the database. Cholera incidence was calculated by using population numbers from Haitian authorities and mapped together with environmental settings by using ArcGIS (ESRI, Redlands, CA, USA). Maps of gridded population density \(^8\), communes, rivers, roads, altitude, internally displaced persons (IDP) camps, and health facilities were obtained from Haitian authorities and the United Nations Stabilization Mission in Haiti (MINUSTAH) website (http://minustah.org).

**Field Surveys**

The first team of epidemiologists from Haiti went to Mirebalais during October 19–24. Then, from November 7–27, epidemiology teams from France and Haiti visited the most affected areas, namely Mirebalais, St-Marc, Gonaïves, Cap Haïtien, St-Michel-de-l'Attalaye, Petite-Rivière-de-l'Artibonite, Ennery, Plaisance, and Port-au-Prince. These visits included interviews with health actors and civilian authorities and investigation of environmental risks among inhabitants and patients from cholera treatment centers.

**Statistics**

To investigate for space–time case clustering, we analyzed the daily case numbers in each Haitian commune from October 16 through November 30 using SaTScan software (Kulldorf, Cambridge, UK). To detect clusters, this software systematically moves a circular scanning window of increasing diameter over the studied region and compares observed case numbers inside the window to the numbers that would be expected under the null hypothesis (random distribution of cases). The maximum allowed cluster size corresponded to 50% of the Haitian population. The statistical significance for each cluster was obtained through Monte Carlo hypothesis testing, i.e., results of the likelihood function were compared with 999 random replications of the dataset generated under the null hypothesis \(^9,10\).

On the basis of these results, we further analyzed risk factors for spread in Ouest, Centre, and Artibonite Departments during October 20–28 using a regression model with adjustment on spatial variability. The initial focus, Mirebalais, was precluded to better estimate the relationship between the epidemic spread and the distance to the epidemic source. Because data on cholera cases were non-normally distributed and thus violated basic assumptions for linear regression, we used a generalized additive model (GAM) \(^11–13\). Furthermore, because of the over-dispersion of the data (variance was greater than mean), we used a quasi-Poisson model (variance = \(c \times \text{mean}\), where \(c\) is an estimated constant) \(^14\). The use of a Poisson model would not have been relevant because the main assumption for Poisson models is that variance equals mean. The GAM was allowed to model the count of cases in each commune, analyzing 1 continuous variable (distance to Mirebalais) and 3 binary variables (location downstream of Meille River, presence of camps of IDP, and commune partially or totally located in coastal plain). The models were adjusted on the population and the spatial distribution of communes. Conditions of use were checked by using classical graphic means. The goodness-of-fit was also assessed by the percentage of explained deviance.

In the communes bordering the Artibonite River, namely Mirebalais, St-Marc, Dessalines, Petite-Rivière-de-l'Artibonite, Grande Saline, Verrettes, Desdunes, and L'Estère, during October 16–31, we searched for synchronizations between communal epidemiologic curves by calculating and testing
Spearman correlation coefficients. Statistical analyses were performed by using R version 2.10.1 software (www.r-project.org/foundation), particularly with the mgcv package (GAM modeling) (11). We compared p values to the probability threshold $\alpha = 0.05$.

![Figure 1](image.png)

**Figure 1.** Location of health centers reporting cholera cases in communes along the Artibonite River on October 20, 2010, Haiti. MINUSTAH, United Nations Stabilization Mission in Haiti.

Initiation
On October 18, the Cuban medical brigades reported an increase of acute watery diarrhea (61 cases treated in Mirebalais during the preceding week) to MSPP. On October 18, the situation worsened, with 28 new admissions and 2 deaths. MSPP immediately sent a Haitian investigation team, which found that the epidemic began October 14. The first hospitalized patients were members of a family living in Meille (also spelled Méyè), a small village 2 km south of Mirebalais (Figure 1). On October 19, the investigators identified 10 other cases in the 16 houses near the index family’s house. Five of the 6 samples collected in Meille from these outpatients, who became sick during October 14–19, yielded *V. cholerae* O1, serotype Ogawa, biotype El Tor. Environmental and water source samples proved negative.

Meille village hosted a MINUSTAH camp, which was set up just above a stream flowing into the Artibonite River. Newly incoming Nepalese soldiers arrived there on October 9, 12, and 16. The Haitian epidemiologists observed sanitary deficiencies, including a pipe discharging sewage from the camp into the river. Villagers used water from this stream for cooking and drinking.

On October 21, the epidemic was also investigated in several wards of Mirebalais. Inhabitants of Mirebalais drew water from the rivers because the water supply network was being repaired. Notably,
prisoners drank water from the same river, downstream from Meille. No other cause was found for the 34 cases and 4 deaths reported in the prison.

On October 31, it was observed that sanitary deficiencies in the camp had been corrected. At the same time, daily incidence of cholera tended to decrease. Afterwards, incidence rose again to reach a second peak on November 10 (Figure 2).

**Spatiotemporal Modeling**

By using SaTScan (Kulldorf), several spatiotemporal clusters were identified (Figure 3): Mirebalais, October 16–19 (p<0.001), and in the Artibonite delta, October 20–28 (p<0.001). Overlapping staggered clusters occurred in the North-West (November 11–29; p<0.001); Port-au-Prince area (November 14–30; p<0.001); and North (November 21–30; p<0.001).

**Epidemic in Lower Artibonite**

The start of the cholera epidemic was explosive in Lower Artibonite (communes of Grande Saline, St-Marc, Desdune, Petite-Rivière-de-l’Artibonite, Dessaline, and Verrettes). It peaked within 2 days and then decreased drastically until October 31 (Figure 2). On October 19, the departmental Direction of Health received a first alert from Bocozel (commune of St-Marc) where 3 children had died from acute watery diarrhea at school. The same day, clusters of patients with severe acute diarrhea and vomiting were admitted to a hospital in Dessalines, and deaths caused by severe diarrhea and vomiting were concomitantly reported in the community. During the next 24 hours, new alerts were registered from ≥10 health centers and hospitals located in each commune covering the lower course of the Artibonite River, from Desarmes (a locality 30 km from the sea) to the seashore (Figure 1). On October 21 at noon, <48 hours after the first alert, 3,020 cholera cases (including 1,766 hospitalizations) and 129 deaths were reported. No cholera cases had been reported in the Lower Artibonite area before October 19. In contrast, almost no cholera cases were recorded in the communes of Saut d’Eau (no case), Boucan Carre (no case), and La Chapelle (2 cases) on October 20 and 21. Only a few hamlets of these 3 communes located between Mirebalais and the Artibonite delta are crossed by the Artibonite River, so population density on its banks is low (Figure 1). Similarly, only 1 case, imported from Lower Artibonite, was reported in Gonaïve on October 20. Gonaïve is built in a floodplain adjacent to the Artibonite delta but watered by a different river running from the north.

The quasi-Poisson GAM model provided a fair goodness-of-fit with deviance explained of 89.4%. Adjusted for population and spatial location, location downstream of the Meille River and commune location in coastal plain were significant risk factors (risk ratios [RRs] 4.91 and 4.60, respectively) but the closeness to Mirebalais was not (Table 1).

A strong correlation was found between the epidemic curves of the communes of the delta but not with that of Mirebalais (Table 2). The correlation was maximum (0.934) between St-Marc and Grande Saline, the 2 seashore communes bordering the main branch of the Artibonite River.

**Table 1.** Adjusted risk ratio of cholera in each commune estimated by the generalized additive model, adjusted for population and spatial variability, Haiti, 2010*

<table>
<thead>
<tr>
<th>Covariate</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location downstream of Meille River</td>
<td>.91 (1.47–16.47)</td>
<td>0.012</td>
</tr>
<tr>
<td>Distance to Mirebalais, km</td>
<td>0.99 (0.94–1.04)</td>
<td>0.594</td>
</tr>
<tr>
<td>Presence of IDP camp</td>
<td>0.10 (0.01–1.12)</td>
<td>0.063</td>
</tr>
<tr>
<td>Commune located in coastal plain</td>
<td>.60 (2.28–9.30)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*RR, adjusted risk ratio; CI, confidence interval; IDP, internally displaced persons.

**Table 2.** Spearman rank correlation between the number of cases in the 8 communes of the Artibonite delta and corresponding p values, Haiti, October 16–31, 2010

<table>
<thead>
<tr>
<th>Commune</th>
<th>L’Estère</th>
<th>Des Dunes</th>
<th>Verrettes</th>
<th>Grande Saline</th>
<th>Petite Rivière de l’Artibonite</th>
<th>Des Salines</th>
<th>St Marc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mirebalais</td>
<td>0.231 (0.389)</td>
<td>0.527 (0.036)</td>
<td>0.276 (0.303)</td>
<td>.480 (0.0509)</td>
<td>.563 (0.023)</td>
<td>0.361 (0.169)</td>
<td>0.459 (0.074)</td>
</tr>
<tr>
<td>St Marc</td>
<td>0.678 (0.004)</td>
<td>0.782 (&lt;0.001)</td>
<td>0.652 (0.006)</td>
<td>0.934 (&lt;0.001)</td>
<td>0.704 (0.002)</td>
<td>0.887 (&lt;0.001)</td>
<td></td>
</tr>
</tbody>
</table>
Spread Out of Artibonite Basin
On October 22, cholera cases were notified in 14 additional communes, most of them in the mountainous regions bordering the Artibonite plain and in Port-au-Prince. We visited several of these communes (Gonaïve, Ennery, Plaisance, Saint-Michel-de-l’Attalaye, and Port-au-Prince) and investigated the circumstances of the onset of cholera outbreaks. In each case, cholera started after the arrival of patients who fled from the ravaging epidemic in the Artibonite delta. There, numerous persons from bordering communes worked in rice fields, salt marshes, or road construction. The deadly epidemic provoked a panic that made them flee back home. Soon after, their communes of origin were experiencing outbreaks. In contrast, the southern half of Haiti remained relatively free of cholera after 6 weeks of epidemics (Figure 3). Spatiotemporal analysis identified slightly staggered clusters occurring from November 11, in North-West, Port-au-Prince, and North Departments, which are roughly equidistant from Artibonite delta. In the North, the largest epidemics occurred in the main cities located in floodplains, especially Cap Haitien and Gonaïve, but numerous deaths were recorded in the mountainous areas between Artibonite plain and northern coast. On November 20, almost 1 month after the first cases had been notified in Saint-Michel-de-l’Attalaye (139,000 inhabitants), we observed several small ongoing cholera outbreaks, striking 1 hamlet after another, leading to 941 cases (including 366 hospitalizations). Forty-one patients died in the hospital, and 110 died in the community. After 1 month, the death rate reached 1.08% in Saint-Michel-de-l’Attalaye.

In Port-au-Prince, the epidemic had 2 phases. For 15 days after the first patients arrived from Artibonite, the epidemic remained moderate with 76 daily cases on average from October 22 through November 5, causing only 77 hospitalizations. Then, the epidemic exploded in Cite-Soleil, a slum located in a floodplain close to the sea. However, after 6 weeks of epidemic, IDP camps were still relatively free of cholera. Despite the earthquake-related damages and the presence of many IDP camps, cholera struck less severely in Port-au-Prince, as demonstrated by incidence rate (0.51% until November 30, compared with 2.67% in Artibonite, 1.86% in Centre, 1.4% in North-West, and 0.89% in North) and cholera-related mortality rate (0.8 deaths/10,000 persons in Port-au-Prince, compared with 5.6/10,000 in Artibonite, 2/10,000 in Centre, 3.2/10,000 in North, and 2.8/10,000 in North-West). Living in the Port-au-Prince metropolitan area was associated with lower incidence (RR 0.51, 95% confidence interval 0.50–0.52; p<10^-7) and lower mortality rates (RR 0.32, 95% confidence interval 0.28–0.37; p<10^-7) than overall Haiti, even when considering unaffected departments.

Discussion
Determining the origin and the means of spread of the cholera epidemic in Haiti was necessary to direct the cholera response, including lasting control of an indigenous bacterium and the fight for elimination of an accidentally imported disease, even if we acknowledge that the latter might secondarily become endemic. Putting an end to the controversy over the cholera origin could ease prevention and treatment by decreasing the distrust associated with the widespread suspicions of a cover-up of a deliberate importation of cholera (15,16). Demonstrating an imported origin would additionally compel international organizations to reappraise their procedures. Furthermore, it could help to contain disproportionate fear toward rice culture in the future, a phenomenon responsible for important crop losses this year (17). Notably, recent publications supporting an imported origin (2) did not worsen social unrest, contrary to what some dreaded (18–20).

Our epidemiologic study provides several additional arguments confirming an importation of cholera in Haiti. There was an exact correlation in time and places between the arrival of a Nepalese battalion from an area experiencing a cholera outbreak and the appearance of the first cases in Meille a few days after. The remoteness of Meille in central Haiti and the absence of report of other incomers make it

<table>
<thead>
<tr>
<th>Comune</th>
<th>Incidence Rate (per 10,000)</th>
<th>RR 0.51 (95% CI) 0.50–0.52 (p&lt;10^-7)</th>
<th>RR 0.32 (95% CI) 0.28–0.37 (p&lt;10^-7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Des Salines</td>
<td>0.872 (0.001)</td>
<td>0.713 (0.002)</td>
<td>0.465 (0.069)</td>
</tr>
<tr>
<td>Petite Rivière de l’Artibonite</td>
<td>0.672 (0.004)</td>
<td>0.675 (0.004)</td>
<td>0.586 (0.017)</td>
</tr>
<tr>
<td>Grande Saline</td>
<td>0.600 (0.014)</td>
<td>0.848 (&lt;0.001)</td>
<td>0.783 (&lt;0.001)</td>
</tr>
<tr>
<td>Verrettes</td>
<td>0.380 (0.147)</td>
<td>0.600 (0.014)</td>
<td></td>
</tr>
<tr>
<td>Des Dunes</td>
<td>0.537 (0.032)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
unlikely that a cholera strain might have been brought there another way. DNA fingerprinting of *V. cholerae* isolates in Haiti (1) and genotyping (24,29) corroborate our findings because the fingerprinting and genotyping suggest an introduction from a distant source in a single event (22).

At the beginning, importation of the strain might have involved asymptomatic carriage by departing soldiers whose stools were not tested for the presence of *V. cholerae*, as the Nepalese army's chief medical officer told the British Broadcasting Corporation (23). The risk for transmission associated with asymptomatic carriage has been known for decades (24), but asymptomatic patients typically shed bacteria in their stool at $\approx 10^6$ *V. cholerae* bacteria per gram of stool (25) and, by definition, have no diarrhea. This small level of shedding would be unlikely to cause interhuman contamination of persons outside the military camp having few contacts, if any, with MINUSTAH peacekeepers. By contrast, considering the presence of sewage pouring from the MINUSTAH camp to the stream, the rapid dissemination of the disease in Meille and downstream, and the probable contamination of prisoners by the stream water, we believe that Meille River acted as the vector of cholera during the first days of the epidemic by carrying sufficient concentrations of the bacterium to induce cholera in persons who drank it. To our knowledge, only infectious doses $>10^4$ bacteria were shown to produce mild patent infection in healthy volunteers, and higher doses are required to provoke severe infections (26,27). Reaching such doses in the Meille River is hardly compatible with the amount of bacteria excreted by asymptomatic carriers, whereas if 1 or several arriving soldiers were incubating the disease, they would have subsequently excreted diarrheal stools containing $10^{-3}$–$10^{4}$ bacteria per liter (25). We therefore believe that symptomatic cases occurred inside the MINUSTAH camp. The negativity of the repeated water samples disfavors the hypothesis of an environmental growth of the bacterium in the Meille stream even if the lack of use of molecular approaches precludes detection of low-level bacterial contamination. Alternatively, a contamination related to sewage discharge could have resulted in transient presence of the bacterium in the water, which could be easily missed by punctual samplings.

Our field investigations, as well as statistical analyses, showed that the contamination occurred simultaneously in the 7 communes of the lower course of the Artibonite River, an area covering 1,500 km², >25 km from Meille. The abrupt upward epidemic curve in the communes bordering Artibonite dramatically contrasts with the progressive epidemic curve in the other communes of Haiti (Figure 2, panel B). In the latter, it took 19 days before the daily number of cases exceeded 1,000 (Figure 2, panel C). Suspected cholera was diagnosed in 7,232 patients during these 19 days. If the transmission in the communes bordering Artibonite had been similar to that of other communes, a comparable number of cases would have occurred in the days preceding the alert on October 20. So many cholera cases would not have remained unnoticed, all the more so as several health facilities of these communes were participating in the MSPP epidemiologic watch. The regression model indicates that the spread of cholera during the peak that occurred from October 20–28 was strongly linked to the Artibonite River and not to the proximity to Mirebalais, as would be expected for road-dependent propagation. This result, as well as the simultaneity of the outbreak onset in 7 communes of Lower Artibonite on October 19, is in accordance with contamination of the Artibonite River in a way that could infect thousands, and kill hundreds, of persons within a few days.

This hypothesis is also sustained by another early investigation during October 21–23 that showed that most affected persons worked or resided in rice fields alongside a stretch of the Artibonite River and that 67% drank untreated water from the river or canals (1). Cholera incubation varies from a few hours to 6 days (26), and the epidemic curve strongly suggests a rapid decrease of the contamination level in the river because the number of new cases and deaths dropped dramatically after only 2 days. A lasting phenomenon would have induced a continuing increase of incidence and a later peak. However, even for a few hours, contamination of a river such as the Artibonite requires a large amount of bacteria. For instance, to reach concentrations of $10^5$ *V. cholerae* bacteria per liter during only 3 hours in the Artibonite River, which usually flows >100 m³/s in October (28), $>10^{14}$ bacteria are required. This level corresponds to the amount of bacteria in 1 m³ of rice-water stools harboring $10^{11}$ *V. cholerae* bacteria per liter. Notably, the fact that the peak in Mirebalais occurred later, on October 26, when daily incidence was dropping dramatically in Lower Artibonite also indicates that a specific mechanism was responsible for the onset of cholera in Lower Artibonite distinct from continuous spread from the primary focus.

Besides the particular circumstance that provoked the Artibonite's outbreak, other factors may have played a role in the severity of the epidemic in Haiti: the absence of immunity among the population, the higher infectivity of epidemic strains shed in human rice-water stools than of environmental strains, and the role of hypervirulent variant strains in provoking epidemics (24,29,30). The recent sequencing of
isolates from Haiti exhibited several structural variations that are hallmarks of the particularly virulent variant strains that have emerged in southern Asia (7).

Whatever its cause, this violent outbreak in Lower Artibonite provoked the flight of persons and resulted in a wave of epidemics that spread centrifugally and overwhelmed the nascent sanitation response. This wave explains the difference between the delayed and progressive starting of epidemics in the south and the immediate impact of cholera in the north. Furthermore, after 6 weeks of epidemics, the IDP camps were still relatively free of cholera. Because the January earthquake led to population displacement, formation of camps, and overcrowding, numerous field actors considered that it was a favorable circumstance for a cholera epidemic. However, in most IDP camps, access to food, safe water, and sanitation was better than in neighboring wards (2,31). This low risk for epidemics after geophysical disaster was already reported in a study summarizing the epidemiologic consequences of >600 disasters (32).

Overall, this report highlights the importance of an accurate field investigation, especially when an epidemic strikes a previously unscathed area or evolves with unusual speed, to ensure an adequate targeting of the response by providing a feedback to the main field actors. Obviously, we have to be cautious with the interpretation that could be made from our results. Although they are compatible with the reports of several journalists who linked the epidemic with the dumping of a septic tank (3), the exact event that provoked the massive contamination of Lower Artibonite cannot be definitively deduced from an epidemiologic study. Rather, identifying the source and the responsibilities falls within the scope and competence of legal authorities. Nonetheless, this epidemic reminds us how critical the management of water and sewage is to prevent cholera spread. To avoid actual contamination or suspicion happening again, it will be important to rigorously ensure that the sewage of military camps is handled properly. Above all else, aid organizations should indeed avoid adding epidemic risk factors to those already existing and respect the fundamental principle of all assistance, which is initially not to harm—primum non nocere.

Acknowledgments

We are grateful to the Haitian Ministry of Public Health and Population authorities, to the Haitian medical teams in each Haitian department, and to the Cuban medical teams in Haiti for collecting the data, and to the French Embassy in Port-au-Prince for supporting this study. Dr Piarroux is a specialist in infectious diseases and parasitology at Université de la Méditerranée. He began studying cholera in various African countries in 1994, when he first experienced a cholera outbreak in a refugee camp in Goma, Democratic Republic of the Congo.

References

Kidney Dopamine Regulates Blood Pressure, Life Span

ScienceDaily (July 21, 2011) — The neurotransmitter dopamine is best known for its roles in the brain—in signaling pathways that control movement, motivation, reward, learning and memory.

Now, Vanderbilt University Medical Center investigators have demonstrated that dopamine produced outside the brain—in the kidneys—is important for renal function, blood pressure regulation and life span. Their studies, published in the July Journal of Clinical Investigation, suggest that the kidney-specific dopamine system may be a therapeutic target for treating hypertension and kidney diseases such as diabetic nephropathy.

Previous studies had suggested a role for dopamine in regulating kidney function and total body fluid volume, "but how that mechanism works was not clear," said Raymond Harris, M.D., chief of the Division of Nephrology and Hypertension at Vanderbilt.

To explore dopamine’s role in the kidney, Harris and Ming-Zhi Zhang, M.D., assistant professor of Medicine at Vanderbilt, eliminated kidney-specific dopamine production in mice (by knocking out a dopamine-generating enzyme only in the kidney) and studied the outcome.

They found that mice lacking kidney dopamine had high blood pressure at baseline and became more hypertensive when they consumed a high-salt diet, suggesting they may be a good model of salt-sensitive (essential) hypertension, Harris said. Alterations in the kidney dopamine system may predispose individuals to hypertension, he noted.

The investigators also showed that elimination of kidney dopamine increased renin production, which activates the angiotensin II system to increase salt and water reabsorption—and produce hypertension.

"These animals retain salt and water when they don’t have sufficient dopamine production in the kidney," Harris said. "Our studies highlight this whole other hormonal system that appears to balance or put the brakes on the renin-angiotensin system."

Currently, the renin-angiotensin system is the major target for treating chronic kidney diseases. Discovering another target—the kidney dopamine system—is exciting, the researchers said. They are exploring whether specific drugs that enhance the kidney dopamine system are effective in blocking hypertension and treating progressive kidney diseases.

The investigators predicted changes in kidney function in the mouse model, but they were "very surprised" to discover that the modified mice only lived about half as long as normal mice (15 months versus 30 months). They found increases in stress-related proteins in the kidney, heart and vasculature, suggesting that elimination of kidney dopamine causes systemic effects, Harris said.

"This kidney-specific dopamine system is not only important for kidney function and blood pressure regulation, but also for the overall health of the animal," Harris said. "If the dopamine system in the kidney is altered, the animals have a markedly shortened life span."

Journal Reference:
Ming-Zhi Zhang, Bing Yao, Suwan Wang, Xiaofeng Fan, Guanqing Wu, Haichun Yang, Huiyong Yin, Shilin Yang, Raymond C. Harris. Intrarenal dopamine deficiency leads to hypertension and decreased longevity in mice. Journal of Clinical Investigation, 2011; 121 (7): 2845 DOI: 10.1172/JCI57324
Proteins Enable Essential Enzyme to Maintain Its Grip On DNA

ScienceDaily (July 21, 2011) — Scientists have identified a family of proteins that close a critical gap in an enzyme that is essential to all life, allowing the enzyme to maintain its grip on DNA and start the activation of genes.

The enzyme, called RNA polymerase, is responsible for setting gene expression in motion in all cells. RNA polymerase wraps itself around the double helix of DNA, using one strand to match nucleotides and make a copy of genetic material.

RNA polymerase cannot fall off of the DNA or stop this process once it starts. If it does, no proteins will be made, and the cell will die.

A team led by Ohio State University researchers demonstrated in a bacterial model that a specific protein binds to two sides of a space in the RNA polymerase molecule at a critical point in its connection to DNA, effectively closing the gap and creating a clamp around the two strands.

In bacteria, two related proteins perform this function. One is NusG, which is required for bacterial growth. Another is RfaH, a virulence factor that gives bacteria their ability to infect and cause disease. Depending on the gene, either NusG or RfaH bridges the critical gap in RNA polymerase in bacteria to maintain the enzyme’s attachment to DNA, the researchers found.

"DNA could be imagined as a cylinder, and RNA polymerase encircles it," said Irina Artsimovitch, associate professor of microbiology at Ohio State and senior author of the research. "Before, we had a structural model where these proteins sit at a site where RNA polymerase contacts the DNA. But even if you see something binding, you still have to prove this binding has a functional consequence. We show here that RNA polymerase forms two halves of a clamp, and these proteins bind in the middle and make the clamp complete."

Though understanding this mechanism was the main goal of the study, the findings could contribute to research in antibiotic development. With these proteins known to have a critical role in supporting cell life, they could function as targets for drugs designed to either kill bacteria or take away their ability to cause disease.

The research is published in the July 22, 2011, issue of the journal *Molecular Cell*.

RNA polymerase is an unusual enzyme because of its processivity, a quality that both requires and enables it to do its extremely long and complicated job perfectly every time, without pausing or making a mistake. Scientists have known that RNA polymerase is processive, but until now didn’t know how it remained so. Because RNA polymerase is universally conserved—meaning it is present and has the same function in all living organisms and has for generations—these findings in bacteria apply to all other forms of life, including humans.

"RNA polymerase has to make very long messages. In humans, RNA chains can be up to 1 million nucleotides long. If RNA polymerase stops prematurely, it loses the RNA chain and has to start over again. To prevent this futile cycle, some factor has to help RNA polymerase to stay bound to the DNA and RNA," Artsimovitch said. "Our major argument is that RNA polymerase can run longer if it makes a ring around the DNA."

Artsimovitch pursued the roles of RfaH and NusG because these proteins, too, are universally conserved, just as the RNA polymerase enzyme is. In other single-celled and also more complex organisms, they have different names than those found in bacteria, but their roles as transcription factors—proteins that control gene expression—are the same. And they are the only family of transcription factors known to be universally conserved.

"It makes sense—if something is universally conserved, it is likely doing something very important," said Artsimovitch, also an investigator in Ohio State’s Center for RNA Biology. She and colleagues conducted a series of genetic and biochemistry experiments in cells and test tubes, respectively, to define the roles of the RfaH and NusG proteins in *Escherichia coli*, their model system. Their findings helped confirm recent reports from other researchers studying single-celled *Archaea* organisms suggesting that the structures of these proteins allow them to close the clamp on RNA polymerase and contribute to its processivity.

There is additional context from Artsimovitch’s work, however, that determines which protein fills the gap.

"So we know the mechanism by which these proteins work is similar in all organisms, but you can have different scenarios," said Anastasia Sevostyanova, a postdoctoral researcher in microbiology at Ohio State and first author of the study.
In most cases, a bacterial cell needs to turn on genes just so it can continue to grow. In those cases, NusG would close the gap. However, under circumstances when specialized control of genes is in order—such as when bacteria infect their human host—then RfaH, the virulence factor, will fill that gap in the RNA polymerase clamp instead.

The researchers hope to further elucidate how other factors from the same universally conserved family of proteins orchestrate the gene expression programs that control cell life.

**Journal Reference:**

**Infant prophylaxis during breastfeeding reduces risk of HIV infection by 71%**
Carole Leach-Lemens
Published: 25 July 2011

Extended use of nevirapine or zidovudine and nevirapine in infants can reduce the risks of HIV transmission through breastmilk by over 70%, Charles van der Horst reported in a late breaker session at the Sixth IAS Conference on HIV Pathogenesis, Treatment and Prevention in Rome last week.

Dr. van der Horst presented findings, on behalf of a collaboration of study investigators from the US, Ethiopia, India, Uganda and Malawi, from a pooled analysis of data from 5,396 mother-infant pairs who participated in five randomised trials to estimate the effectiveness of infant nevirapine prophylaxis in preventing breast-milk HIV transmission in HIV-negative infants at birth.

In resource-poor settings mother-to-child transmission of HIV continues to be a major cause of death and disease. Breastfeeding accounts for about a third of the estimated more than 420,000 children infected each year. Fifty percent of these children will die before they reach two years of age.

Women are faced with a dilemma. While breastfeeding provides protection and is associated with decreased mortality and disease in the first year of life compared to formula, the longer they breastfeed the greater the risk of HIV transmission: 68% of all HIV infections among infants who breastfeed happen after six months of age.

Since safe and affordable replacement options to breastfeeding are severely limited in most resource-poor settings, effective strategies to prevent transmission through breastfeeding are critical.

Maternal ART, when available, can be protective against transmission. In 2009 an estimated 53% of identified pregnant HIV-infected women in low- and middle-income countries got ART. Lower maternal CD4 cell counts are associated with a greater probability of MTCT and death, and many women in resource-poor settings present late for antenatal care. For ART to be effective in PMTCT viral loads need to be undetectable, which may take several weeks after starting antiretroviral treatment.

Maternal and infant single-dose and infant extended-dose nevirapine offer important alternative means of protection for the infants of HIV-infected breastfeeding mothers.

Results from these randomised clinical trials have shown daily nevirapine to be effective in preventing HIV transmission through breastmilk. These results, among others, led the World Health Organization (WHO) to change its guidelines in 2010.

Exclusive breastfeeding for six months with the introduction of complementary foods for the next six months is now recommended. Breastfeeding should stop at the end of 12 months, if feasible. Rapid weaning is no longer advised.

The trials included in the pooled analysis comprised:

- Six-week extended nevirapine (SWEN): Three separate but comparable studies in Ethiopia, India and Uganda where six weeks of daily infant nevirapine was used for prophylaxis but no maternal antenatal prophylaxis;
- Post-exposure prophylaxis of the infant (PEPI) in Malawi: No antenatal prophylaxis was given; nevirapine for 14 weeks and the same but with daily nevirapine were compared, during birth the mothers got single-dose nevirapine and their infants got single-dose nevirapine and one week of zidovudine; and
- Breastfeeding, antiretrovirals and nutrition (BAN) trial in Malawi: Daily infant nevirapine given for 28 weeks was compared to maternal ART; at delivery all infants and mothers got single-dose nevirapine and one week of zidovudine and lamivudine.

The SWEN and PEPI trials included women of all CD4 cell counts, whereas the BAN trial only included women with CD4 cell counts over 200 cells/mm³.
In the analysis Dr. van der Horst and colleagues compared the four daily regimens: nevirapine for six weeks, 14 weeks, or 28 weeks, or nevirapine plus zidovudine for 14 weeks.

In the six-week regimen (SWEN) the estimated risk for transmission was 1.6% compared to 3.4% for the control at the end of treatment at the age of six weeks.

In the 14-week regimens (PEPI) the estimated risks for transmission for nevirapine alone and nevirapine plus zidovudine were 1.9% and 2.3%, respectively compared to 7.3% for the control.

At the end of 28 weeks (BAN) the longer the duration of nevirapine, the lower the estimated risk of transmission.

Infants infected within the first week, those with indeterminate specimens at birth or six months, those who died within the first week after birth and those whose mothers’ CD4 cell counts were under 200 cells/mm$^3$ were excluded from the pooled analysis.

The primary outcome of the analysis was infection or death by 203 days.

The estimated cumulative risk of HIV infection among infants uninfected at birth was 5.8% (95% CI: 4.0 to 7.6), 3.7% (95% CI: 2.3 to 5.1), 4.8% (95% CI: 3.2 to 6.4) and 1.8% (95% CI: 0.8 to 2.8), p<0.001 for the six week, 14 week nevirapine alone, 14 week dual prophylaxis regimen and 28 week nevirapine regimen, respectively.

Women with a baseline CD4 cell count between 200 cells/mm$^3$ and 350 cells/mm$^3$ had a two-fold higher rate of their infants becoming infected than those with CD4 cell counts over 350 cells/mm$^3$. In addition the more the infant weighed at birth, the less likely they were to become infected.

After adjusting for maternal baseline CD4 cell count and infant birth weight according to trial site nevirapine reduced the rate of HIV infection by 71% (95% CI: 58-80, p<0.001) and the rate of HIV infection or death by 58% (95% CI: 45-69, p<0.001).

Dr. van der Horst concluded “extended prophylaxis with nevirapine or with nevirapine and zidovudine significantly reduces postnatal HIV-infection; the longer the duration of prophylaxis, the greater the reduction in the risk of infection.”

Reference
Hudgens, M et al. Pooled individual data analysis of five randomized trials of infant nevirapine prophylaxis to prevent HIV-1 transmission through breast milk. The Sixth IAS Conference on HIV Pathogenesis, Treatment and Prevention, Rome, 2011, abstract WELBC03.

Drug prices to plummet in wave of expiring patents
By LINDA A. JOHNSON, AP Business Writer
Monday, July 25, 2011
In this June 6, 2011 photo, Ray and Jo Kelly relax on a swing in front of their home in Conklin, Mich., where they live in retirement. The two both take Lipitor and look forward to having extra money when the drug is replaced with a generic in the fall.

The cost of prescription medicines used by millions of people every day is about to plummet.

The next 14 months will bring generic versions of seven of the world’s 20 best-selling drugs, including the top two: cholesterol fighter Lipitor and blood thinner Plavix.

The magnitude of this wave of expiring drugs patents is unprecedented. Between now and 2016, blockbusters with about $255 billion in global annual sales will go off patent, notes EvaluatePharma Ltd., a London research firm. Generic competition will decimate sales of the brand-name drugs and slash the cost to patients and companies that provide health benefits.

Top drugs getting generic competition by September 2012 are taken by millions every day: Lipitor alone is taken by about 4.3 million Americans and Plavix by 1.4 million. Generic versions of big-selling drugs for blood pressure, asthma, diabetes, depression, high triglycerides, HIV and bipolar disorder also are coming by then.

The flood of generics will continue for the next decade or so, as about 120 brand-name prescription drugs lose market exclusivity, according to prescription benefits manager Medco Health Solutions Inc.

"My estimation is at least 15 percent of the population is currently using one of the drugs whose patents will expire in 2011 or 2012," says Joel Owerbach, chief pharmacy officer for Excellus Blue Cross Blue Shield, which serves most of upstate New York.

Those patients, along with businesses and taxpayers who help pay for prescription drugs through corporate and government prescription plans, collectively will save a fortune. That’s because generic drugs typically cost 20 percent to 80 percent less than the brand names.

Doctors hope the lower prices will significantly reduce the number of people jeopardizing their health because they can’t afford medicines they need.
Dr. Nieca Goldberg, director of The Women's Heart Program at NYU Langone Medical Center in Manhattan, worries about patients who are skipping checkups and halving pills to pare costs.

"You can pretty much tell by the numbers when I check the patient's blood pressure or cholesterol levels," that they've not taken their medications as often as prescribed, she says.

Even people with private insurance or Medicare aren't filling all their prescriptions, studies show, particularly for cancer drugs with copays of hundreds of dollars or more.

The new generics will slice copayments of those with insurance. For the uninsured, who have been paying full price, the savings will be much bigger.

Daly Powers, 25, an uninsured student who works two part-time jobs at low wages, says he often can't afford the $220 a month for his depression and attention deficit disorder pills. He couldn't buy either drug in June and says he's struggling with his Spanish class and his emotions. He looks forward to his antidepressant, Lexapro, going generic early next year.

"It'd make all the difference in the world," says Powers, of Bryan, Texas.

Generic medicines are chemically equivalent to the original brand-name drugs and work just as well for nearly all patients.

When a drug loses patent protection, often only one generic version is on sale for the first six months, so the price falls a little bit initially. Then, several other generic makers typically jump in, driving prices down dramatically.

Last year, the average generic prescription cost $72, versus $198 for the average brand-name drug, according to consulting firm Wolters Kluwer Pharma Solutions. Those figures average all prescriptions, from short-term to 90-day ones.

Average copayments last year were $6 for generics, compared with $24 for brand-name drugs given preferred status by an insurer and $35 for nonpreferred brands, according to IMS Health.

Among the drugs that recently went off patent, Protonix, for severe heartburn, now costs just $16 a month for the generic, versus about $170 for the brand name. And of the top sellers that soon will have competition, Lipitor retails for about $150 a month, Plavix costs almost $200 a month and blood pressure drug Diovan costs about $125 a month. For those with drug coverage, their out-of-pocket costs for each of those drugs could drop below $10 a month.

Jo Kelly, a retired social worker in Conklin, Mich., and her husband, Ray, a retired railroad mechanic, each take Lipitor and two other brand-name medicines, plus some generic drugs. Both are 67, and they land in the Medicare prescription "doughnut hole," which means they must pay their drugs' full cost by late summer or early fall each year. That pushes their monthly cost for Lipitor to about $95 each, and their combined monthly prescription cost to nearly $1,100.

Generic Lipitor should hit pharmacies Nov. 30 and cost them around $10 each a month.

"It would be a tremendous help for us financially," she says. "It would allow us to start going out to eat again."

For people with no prescription coverage, the coming savings on some drugs could be much bigger. Many discount retailers and grocery chains sell the most popular generics for $5 a month or less to draw in shoppers.

The impact of the coming wave of generics will be widespread — and swift.

Insurers use systems that make sure patients are switched to a generic the first day it's available. Many health plans require newly diagnosed patients to start on generic medicines. And unless the doctor writes "brand only" on a prescription, if there's a generic available, that's almost always what the pharmacist dispenses.

"A blockbuster drug that goes off patent will lose 90 percent of its revenue within 24 months. I've seen it happen in 12 months," says Ben Weintraub, a research director at Wolters Kluwer Pharma Solutions. The looming revenue drop is changing the economics of the pharmaceutical industry.

In the 1990s, big pharmaceutical companies were wildly successful at creating pills that millions of people take every day for long-term conditions, from heart disease and diabetes to osteoporosis and chronic pain. The drugs are enormously profitable compared with drugs that are prescribed for short-term ailments.

The patents on those blockbusters, which were filed years before the drugs went on sale, last for 20 years at most, and many expire soon.

In recent years, many drug companies have struggled to develop new blockbuster drugs, despite multibillion-dollar research budgets and more partnerships with scientists at universities and biotech companies. The dearth of successes, partly because the "easy" treatments have already been found, has turned the short-term prognosis for "big pharma" anemic.
"The profit dollars that companies used to reinvest in innovation are no longer going to be coming," warns Terry Hisey, life sciences leader at consultant Deloitte LLP’s pharmaceutical consulting business. He says that raises "long-term concerns about the industry's ability to bring new medicines to market."

But pharmaceutical companies can save billions when they stop promoting drugs that have new generic rivals, and U.S. drug and biotech companies are still spending more than $65 billion a year on R&D.

Drug companies have received U.S. approval for 20 drugs this year and expect approval for other important ones the next few years. Eventually, those will help fill the revenue hole.

For now, brand-name drugmakers are scrambling to adjust for the billions in revenue that will soon be lost. Typically, they raise prices 20 percent or more in the final years before generics hit to maximize revenue. Some also contract with generic drugmakers for "authorized generics," which give the brand-name company a portion of the generic sales.

Brand-name companies also are trimming research budgets, partnering with other companies to share drug development costs and shifting more manufacturing and patient testing to low-cost countries. Pharmaceutical companies have cut about 10 percent of U.S. jobs in four years, from a peak of about 297,000 to about 268,000, according to Labor Department data. Nearly two-thirds of the cuts came in the last 1 1/2 years, partly because of big mergers that were driven by the need to bulk up drugs in development and boost profits in the short term by cutting costs.

Drug companies also are trying to grow sales by putting more sales reps in emerging markets, such as China and India, and by diversifying into businesses that get little or no generic competition. Those include vaccines, diagnostic tests, veterinary medicines and consumer health products.

As the proportion of prescriptions filled with generic drugs jumped to 78 percent in 2010, from 57 percent in 2004, annual increases in prescription drug spending slowed, to just 4 percent in 2010. According to the Generic Pharmaceutical Association, generics saved the U.S. health care system more than $824 billion from 2000 through 2009, and now save about $1 billion every three days.

The savings are only going to get greater as our overweight population ages. People who take their medicines regularly often avoid costly complications and hospitalizations, says AARP’s policy chief, John Rother, which produces even bigger savings than the cheaper drugs.

In addition, many patients taking a particular brand-name drug will defect when a slightly older rival in the same class goes generic.

Global sales of Lipitor peaked at $12.9 billion in 2006, the year Zocor, an older drug in the statin class that reduces bad cholesterol, went generic. Lipitor sales then declined slowly but steadily to about $10.7 billion last year. That still will make Lipitor the biggest drug to go generic.

For patients, it’s a godsend.

Douglas Torok, 59, of Erie, Pa., now spends nearly $290 every three months for insulin for his Type 2 diabetes, plus four daily pills — Lipitor, Plavix and two generics — for his blood pressure and cholesterol problems. The $40,000-a-year foundry supervisor fears not being able to cover the out-of-pocket costs when heretires and doesn’t have a generous prescription plan.

In the meantime, once Lipitor and Plavix get generic competition his copayments will plunge. "I will pay $16 for 90 days," says Torok, who hopes to travel more. "It's a big deal for me on my income."

HIV/AIDS: Adult male circumcision – new developments

ROME, 25 July 2011 (PlusNews) – Medical male circumcision has been a World Health Organization (WHO)-endorsed HIV prevention method for more than four years, with most countries still using relatively expensive surgical procedures that require anaesthetic, at least a couple of health workers and a six-week healing period. However, several new devices could revolutionize the amount of time, labour and money involved, enabling countries to rapidly scale up their programmes.

WHO has approved three devices – the Gomco Clamp, the Mogen Clamp and the Plastibell – for infant male circumcision, but none for adult male circumcision. In February 2011, the organization developed a framework for the clinical evaluation of devices for adult male circumcision.

Some of the devices under investigation include:

**The Shang Ring** – Developed in China, the Shang Ring comprises an inner and outer ring; the foreskin is placed between them and cut off, leaving the glans exposed during the seven-day healing period, after which the device is removed.

Clinical trials in China have found the device to be safe, and a pilot study in western Kenya’s Homa Bay found six mild adverse events – including skin injury, oedema and mild infection – when the device was tested on 40 HIV-negative men.

Several more studies on the Shang Ring are ongoing, including in Kenya and Uganda, on acceptability, safety and randomized controlled trials in Kenya and Zambia comparing it to surgical procedures.

**The PrePex Device** – Developed in Israel, the PrePex uses two rings and an applicator to restrict blood supply to the foreskin, which is removed, together with the device, after seven days. This method requires no anaesthesia.

A study of 40 men in Rwanda found one adverse event at removal of the device and a healing time of 17 days. More studies are ongoing and planned in Rwanda and Zimbabwe. The Rwandan government plans to scale up male circumcision using the PrePex device.

**The Tara KLamp** – Developed by Gurcharan Singh in Malaysia, the Tara KLamp has been widely used there for the circumcision of boys, including in public sector hospitals and circumcision campaigns. The device clamps on the foreskin so that the blood supply is cut off, and after seven to 10 days the foreskin is supposed to fall off with the clamp, but sometimes the clamp has to be surgically removed.

It has also been controversially promoted in Lesotho and South Africa. In 2009, a randomized controlled trial in Orange Farm, South Africa, found adverse events of 37 percent in the 35 men in the Tara KLamp study, against 3.4 percent in the 34 men in the surgical arm. Men circumcised using the KLamp also reported worse pain. The trial was stopped early due to the unacceptably high rate of adverse events, with the researchers noting that, “given the high rates of adverse events in this study and the low number of available studies, we strongly caution against the use of the TK for young adults, and we recommend careful evaluation of the procedure when performed on children”.

Nevertheless, Zulu king Goodwill Zwelithini in 2009 endorsed the KLamp for use in the traditional circumcision of boys in KwaZulu-Natal. It was used in about a quarter of the 35,000 circumcisions conducted; little data has emerged on complications. South African activist group, the Treatment Action Campaign declined to endorse the KLamp, stating that it was “simply too risky for use on male adults and should not be used in the public health system”.

In June 2011, the South African government announced that it would not be using the Tara KLamp as part of its official male circumcision scale-up. According to WHO, no further clinical studies of the Tara KLamp are planned.
'Syphilis Plague' Makes Comeback; Tenfold Increase from 1993-2009 in Canada

*Toronto Star*, (07.15.2011)

Syphilis in Canada has fought its way back from near elimination 13 years ago, according to the Public Health Agency of Canada (PHAC), with cases increasing nearly tenfold from 1993 to 2009. Of the 1,683 documented cases in 2009, 1,501 affected men.

PHAC spokesperson Jana Lerner attributes the spike to factors including incorrect condom use and inconsistent safe sex practices. "Sexually transmitted infections, including syphilis, continue to be a public health concern in Canada," she said.

To combat the increases, provinces are ramping up innovative marketing campaigns. Alberta's faux dating website, plentyofsyphs.com, bills itself as a "one-stop syphilis shop," goading visitors to "Start laughing, flirting and getting infected in seconds with sexy single simmering with syphilis."

PHAC is distributing syphilis prevention information, including audio-visual materials from an online symposium entitled "Return of the Syphilis Plague."

Upwards of 90 percent of Toronto's 508 syphilis cases in 2010 were in men — 50 to 70 percent of them HIV-positive, said Bruce Clarke of Toronto Public Health (TPH). Clarke credits the rates to the sero-sorting practice of some HIV-positive men, whereby infected men have sex with one another, assuming condoms are not necessary since both parties are HIV-positive. They may unsuspectingly be spreading syphilis, he explained.

TPH, AIDS Committee of Toronto and the local health ministry are using mock 1950s B-movie posters to warn HIV-infected men of the "Attack of the Cursed Syphilis." In the fall, TPH, Toronto's Hassle Free Clinic, Ottawa Public Health and local government will debut ads encouraging men to get tested for HIV and syphilis.

Halifax infectious-disease specialist Dr. Todd Hatchette noted the impact of syphilis countrywide, pointing out increasing instances in eastern Canada. "It's hard to know [why]. Probably it is linked to increased unsafe practices, multiple partners [and] anonymous sex," said Hatchette.

New Drug Adds to Arsenal Against AIDS

*Agence France Presse*, (07.14.2011)

The new HIV drug rilpivirine is safe and effective and has fewer side effects than efavirenz when used in combination therapy, two recent studies found.

Used in combination regimens, nevirapine and efavirenz (Sustiva) are equally effective in viral suppression, but they can cause severe side effects, which is why researchers are investigating possible substitutes. Like them, rilpivirine is a non-nucleoside reverse transcriptase inhibitor.

Marketed by Tibotec as Edurant, rilpivirine was compared with efavirenz in various regimens in two studies involving nearly 1,400 patients in 21 countries.

In the first study, initial response rates (viral load under 50 copies/mL, defined by intention-to-treat time to loss-of-virological-response algorithm [ITT-TLOVR]) were 86 percent for rilpivirine-based therapy and 82 percent for efavirenz-based therapy, and CD4 cell count increases were similar between the groups. Incidence of virological failure was slightly higher in the rilpivirine than efavirenz group (7 percent vs. 5 percent), though fewer discontinued treatment on rilpivirine than efavirenz due to adverse events (4 percent vs. 7 percent). Grade 2-4 treatment-related adverse events were less common with rilpivirine than efavirenz (16 percent vs. 31 percent), and lipid increases were significantly lower on rilpivirine than efavirenz (p<0.0001).

At 48 weeks, rilpivirine proved non-inferior in efficacy to efavirenz using a 12 percent margin on logistic regression analysis, the study found.

In the second study comparing rilpivirine-based with efavirenz-based therapy, response rates (less than 50 copies/mL ITT-TLOVR) were 83 percent for both confirmed at 48 weeks. Rilpivirine proved non-inferior in efficacy compared with efavirenz (also 12 percent margin), though incidence of virological failure was higher for rilpivirine (13 percent vs. 6 percent; 11 percent vs. 4 percent ITT-TLOVR). Grade 2-4 adverse events and discontinuations due to AEs were less common for rilpivirine than efavirenz (Grade 2-4: 16 percent vs. 31 percent; discontinuations: 2 percent vs. 8 percent).

Rilpivirine had a more favorable safety and tolerability profile than efavirenz, though a higher virological failure rate, and was non-inferior in efficacy, the study authors concluded.

The studies, "Rilpivirine Versus Efavirenz with Two Background Nucleoside or Nucleotide Reverse Transcriptase Inhibitors in Treatment-Naïve Adults Infected with HIV-1 (THRIVE): A Phase 3, Randomized, Non-Inferiority Trial" and "Rilpivirine Versus Efavirenz with Tenofovir and Emtricitabine in..."
Treatment-Naïve Adults Infected with HIV-1 (ECHO): A Phase 3 Randomized Double-Blind Active-Controlled Trial,” were published in Lancet (2011;378(9787):229-237 and 238-246, respectively).

**Haitian Cholera Epidemic Worsening With Start Of Rainy Season**
According to the Haitian government, more than 5,800 people have died of cholera since the epidemic began in October, and health care workers have seen an increase in cases "[w]ith the rainy season now in progress," the Los Angeles Times reports (Gaestel, 7/24).

Boston-based Partners in Health, which has been active in Haiti for decades, said "nearly 15,000 patients sought treatment for the disease at its clinics in June. That is quadruple the number treated in April – and many health workers are expecting the situation to get worse as heavy rains cause flooding that could contaminate drinking water," the Boston Globe writes (Satija, 7/24).

In related news, on Friday, "European Union (E.U.) health officials ... warned [pdf] travelers about a risk of contracting cholera in the Dominican Republic, a magnet for tourists, while the World Health Organization (WHO) said cholera outbreaks along Africa’s Congo River have killed 271 people,” according to CIDRAP News (Roos, 7/22).

**Specialized regulatory T cell stifles antibody production centers**
**Discovery has potential implications for cancer, autoimmune disease**
HOUSTON — A regulatory T cell that expresses three specific genes shuts down the mass production of antibodies launched by the immune system to attack invaders, a team led by scientists at The University of Texas MD Anderson Cancer Center reported online in the journal *Nature Medicine*.

"Regulatory T cells prevent unwanted or exaggerated immune system responses, but the mechanism by which they accomplish this has been unclear," said paper senior author Chen Dong, Ph.D., professor in MD Anderson’s Department of Immunology and director of the Center for Inflammation and Cancer.

"We've identified a molecular pathway that creates a specialized regulatory T cell, which suppresses the reaction of structures called germinal centers. This is where immune system T cells and B cells interact to swiftly produce large quantities of antibodies," Dong said.

The discovery of the germinal center off-switch, which comes two years after Dong and colleagues identified the mechanisms underlying a helper T cell that activates the centers, has potential implications for cancer and autoimmune diseases.

"In some types of cancer, the presence of many regulatory T cells is associated with poor prognosis," Dong said. "The theory is those cells suppress an immune system response in the tumor's microenvironment that otherwise might have attacked the cancer."

However, in B cell lymphomas, overproliferation and mutation of B cells are the problems, Dong said. Hitting the regulatory T cell off-switch might help against lymphomas and autoimmune diseases, while blocking it could permit an immune response against other cancers.

**Antibody production central**
Germinal centers are found in the lymph nodes and the spleen. They serve as gathering points for B and T cell lymphocytes, infection-fighting white blood cells.

When the adaptive immune system detects an invading bacterium or virus, B cells present a piece of the invader, an antigen, to T cells. The antigen converts a naïve T cell to a helper T cell that secretes cytokines, which help the B cells expand and differentiate into specialized antibodies to destroy the intruder.

"Germinal centers have mostly B cells with a few helper T cells to regulate them. The B cells mutate to make high-affinity antibodies and memory B cells for long-term immunity. The cell population in the germinal center structures replicates in an average of several hours, one of the fastest rates of cell replication known in mammals," Dong said.

**Tracking down specialized T cell**
In the *Nature Medicine* paper, Dong and colleagues found that a subgroup of regulatory T cells that expresses two genes, Bcl-6 and CXCR5, moves into germinal centers in both mice and humans, where they have access to B cells.

(Bcl-6 produces a protein called a transcription factor, which moves into the cell nucleus to regulate other genes. CXCR5 is a receptor protein for a signaling molecule called CXCL13.)

They also found that the Bcl-6/CXCR5 T cells aren’t produced in the thymus, with other T cells, but are generated by regulatory T cell precursor cells that express Foxp3, another transcription factor.
Knocking out the regulatory T cells that express all three proteins in mice resulted in increased germinal center production of antibodies. They named this key T cell the T follicular regulatory cell, or Tfr.

In a 2009 paper in the journal *Science*, the researchers found that naïve T cells that expressed Bcl-6 and CXCR5 also gathered in the B cell zone of germinal centers. Expression of Bcl6 converted the T cell into a T follicular helper (Tfh) cell that launches antibody production in the germinal centers. With Tfr turning germinal centers off and Tfh turning them on, we could potentially regulate antibody production, Dong noted. Increasing Tfr production could be a new approach to treating autoimmune inflammatory disorders, such as lupus and rheumatoid arthritis.

**Scavenger Cells Accomplices to Viruses**

*ScienceDaily* (July 25, 2011) — Mucosal epithelia are well-protected against pathogenic germs. However, individual viruses, such as the HI virus, still manage to enter the body via the mucous membrane somehow. Cell biologists from the University of Zurich have now identified a new infection mechanism, demonstrating that the viruses use the body’s own scavenger cells for the infection. The new findings are important for cancer-gene therapy and the development of antiviral medication.

Mucosal epithelia do not have any receptors on the outer membrane for the absorption of viruses like hepatitis C, herpes, the adenovirus or polio, and are thus well-protected against pathogenic germs. However, certain viruses, such as the human immunodeficiency virus HIV, still manage to enter the body via the mucous membrane. Just how this infiltration occurs on a molecular level has been a mystery. Three hypotheses were discussed: firstly, that it’s caused by mechanical damage to the mucous membrane; secondly, the presence of previously unknown receptors on the mucous membrane cells; and, thirdly, that the viruses are smuggled in via a kind of Trojan horse. Now, for the first time, cell biologists from the University of Zurich have succeeded in identifying the infection mechanism for adenoviruses.

In the recently published online magazine *Nature Communications*, Verena Lütschg and cell biologists from the Institute of Molecular Biology headed by Urs Greber reveal how type-5 adenoviruses in the lung epithelia utilize an immune response triggered by the infection for the progression of the infection: Adenoviruses use scavenger cells and their subsequent production of antiviral cytokines as a door-opener for the infection of the lung epithelial cells.

**Exposure of shielded receptors**

Antiviral cytokines play a key role in immunological reactions and trigger inflammatory responses, for instance. They induce the epithelial cells to expose certain receptors that are shielded under normal conditions and thus activate immune cells in defense. For healthy people, an infection of the lung with type-5 adenoviruses is harmless as they merely cause a cold. Under very stressful situations or in the case of chronic respiratory diseases, however, adenoviruses can cause severe, acute infections that can sometimes be fatal.

The recently identified infection mechanism can serve as a model for how the pathogens penetrate the mucosal epithelial cells and enter the body. However, it is also crucial from a therapeutic point of view. Type-5 adenoviruses are already used very often as transport vehicles in cancer-gene therapy today. Knowing the transport route will help develop both this gene therapy and specifically acting cancer treatment further.
Fault in Immune Memory Causes Atopic Eczema and Psoriasis, Study Finds

ScienceDaily (July 22, 2011) — Scientists from the Centre for Allergy and Environment in Munich (ZAUM), the Helmholtz Zentrum München and the Technische Universität München believe they have discovered the causes of atopic eczema and psoriasis. The results of the studies have been published in the New England Journal of Medicine.

The findings of a research study conducted by Stefanie and Kilian Eyerich show that both diseases are caused by an impaired immunological memory.

The couple, who are engaged in research at the Helmholtz Zentrum München and the Department of Dermatology and Allergology Biederstein, Technische Universität München (TUM), based their study on a rare group of patients who suffer from both diseases. As their results show, the T-cells of the immune system in the skin activate an inflammatory programme that causes either atopic eczema or psoriasis. Professor Ring, co-author and Director of Department of Dermatology and Allergology Biederstein believes that "this study highlights the critical role of T-cells in psoriasis."

The scientists now aim to find out which T-cell molecules are responsible for triggering these diseases. "Clearly, future therapy strategies should focus on the impairment of the immunological memory," says Professor Carsten Schmidt-Weber, Director of ZAUM.

- T-cells together with the B-cells form the body's immunological memory. They initiate an immune response when they recognize substances that are foreign to the body.
- In the case of atopic eczema / neurodermatitis, the T-cells recognise substances that trigger an immune response: these include components of pollen, house-dust mites and also bacteria. In the case of psoriasis, it remains unclear which molecules are responsible for the response.

The Origin of Malaria: The Hunt Continues

ScienceDaily (July 25, 2011) — The agent of malaria has been found in the greater spot-nosed monkey, also known as putty-nosed monkey (Cercopithecus nictitans), a small African primate derived from a line different to that of humans, gorillas and chimpanzees. This discovery challenges current thinking on the origin of the parasite and introduces a key element in the fight against malaria: knowing how it has adapted to the human species will make it possible to target its weaknesses.

This work stems from research carried out by CNRS researchers in association with other organizations(1) and is published on the 4 July 2011 in the journal PNAS.

Malaria, also known as paludism, is one of the greatest global scourges. This pathiology, which causes a million human deaths each year, is especially rampant in Africa. The question of whether the primary infection originated from rodents or birds has long remained unanswered. Also found in gorillas, it was thought that the parasite was specific to hominids(2).

By working on the subject, a team of CNRS researchers headed by Franck Prugnolle and François Renaud of the Laboratoire MIVEGEC(1)(CNRS/IRD/Université Montpellier 1), jointly with the Centre International de Recherches Médicales de Franceville in Gabon, and in collaboration with other organizations(4), has demonstrated the presence of Plasmodium falciparum, the agent of malaria, in the greater spot-nosed monkey (Cercopithecus nictitans), a small African monkey derived from a line
different to that of humans. The origin of the parasite probably predates the origins of the African hominids line.

The presence of *Plasmodium falciparum* in this Old World Monkey opens the way to the analysis of the genome of the parasite found in this species. Comparing its sequence with that (already known) of *falciparum* in humans will enable researchers to discover the molecular signatures of the human parasite and to find out how it has adapted to humans. Knowing the weaknesses of the parasite will be a major asset in combating malaria.

(1)Centre International de Recherches Médicales de Franceville au Gabon, IRD, Université Montpellier 1, Université de la Méditerranée, Université de Toulouse, University of California and Université de Brazzaville.

(2)The hominids line comprises two branches: humans and large monkeys (gorillas, chimpanzees and orangutans).

(3)Laboratoire "Maladies Infectieuses et Vecteurs: Ecologie, Génétique, Evolution et Contrôle"

(4)Université de la Méditerranée, Université de Toulouse, University of California and Université de Brazzaville.

**Journal Reference:**


**Identical Virus, Host Populations Can Prevail for Centuries**

ScienceDaily (July 22, 2011) — A Woods Hole Oceanographic Institution (WHOI) scientist, analyzing ancient plankton DNA signatures in sediments of the Black Sea, has found for the first time that the same genetic populations of a virus and its algal host can persist and coexist for centuries. The findings have implications for the ecological significance of viruses in shaping algae ecosystems in the ocean, and perhaps fresh water as well.

"The finding that the DNA of viruses and algal host cells can be preserved in the geological records is of great interest to microbial ecologists," said Marco Coolen of WHOI's Marine Chemistry and Geochemistry department and author of the study, which appears in the July 22 issue of *Science.* "This offers unprecedented insights into long-term algal, viral, and host population dynamics between globally important algae and their viral pathogens in the ocean."

In examining the 7,000-year continuous genetic record in sediments underlying the Black Sea, Coolen discovered that the DNA of both the Coccolithovirus and its host, *Emiliania huxleyi,* a phytoplankton that plays a major role in the global carbon cycle, have been preserved over thousands of years.

"Biologists now for the first time have a picture of long-term viral/host dynamics in the ocean," Coolen said. Previous laboratory work had confirmed such co-existence for only a few successive years.

Coolen added that much longer virus/host records such as the ones he studied, for the first time "could answer important questions, such as: 'What factors are involved in controlling viral infection of the globally important marine algae and how long can the same host and virus populations co-exist?' and 'Were past algal populations only controlled by the prevailing environmental conditions or did viruses also play an important role in shaping past algal community structures?'

The latter question is of particular interest, Coolen said, because "nobody has long-term records of viruses. Ecological shifts in past algal communities are generally explained by changes in climate and environmental conditions." Now it seems possible, he said, that viruses also played an important role in shaping past algal communities.

This is important for *E. huxleyi,* which performs photosynthesis—"just like plants," says WHOI scientist Benjamin Van Mooy. "They consume carbon dioxide." In doing so, they reduce the amount of CO2 released into the atmosphere. They form a calcium carbonate shell, also helping to regulate the carbon cycle.

But DNA viruses of the genus Coccolithovirus kill off large populations of *E. huxleyi,* particularly in the North Atlantic. Van Mooy has traced this phenomenon to lipids, or fatty compounds, in certain viruses. If viruses are killing off phytoplankton, this can increase greenhouse emissions, Van Mooy suggests. "That's important because if viruses infect a whole bunch of cells, then they can't perform photosynthesis, they can't take up carbon dioxide."

Coolen says his data buttress Van Mooy's work by suggesting a significant role for viruses in affecting the algal population and carbon cycling in the past. He observed, for example, major shifts in the types of
Coccolithovirus and *E. huxleyi* in the Black Sea sediments over the centuries. Environmental conditions almost certainly had a role in selecting successful *E. huxleyi* genotypes, but Coolen believes viruses may have as well.

"Until now, shifts in past plankton species identified through the microscopic analysis of preserved diagnostic cellular fossils have mainly been linked to changes in environmental conditions and climate," Coolen said. "However, understanding the viral role in controlling past algal stocks is necessary to improve the interpretation of past climate records. This can now be studied using ancient DNA methods."

One thing that enabled Coolen to study sediments so far back in time was the continuous absence of oxygen in the bottom waters of the Black Sea the last 7,500 years. "This lack of oxygen facilitated the preservation of organic material in general and ancient viral and algal plankton DNA in particular," he said.

In addition, unpublished data from Coolen's lab "show that Black Sea sediments older than 7,500 years contain well-preserved DNA of a different suite of algae adapted to lower salinities and freshwater environments and likely also DNA of their viral pathogens," he said. "In other words, comparable studies could most likely be employed in a wide variety of marine and lake ecosystems.

"In a different and broader context," he adds, "it will perhaps be possible to reconstruct the historical spread of human viral diseases since a variety of human viral infections are also caused by DNA viruses."

The research was funded by grants from the National Science Foundation (NSF) and a grant from the Andrew W. Mellon Foundation.

**Journal Reference:**

**IAS 2011: New Integrase Inhibitor Dolutegravir Looks Potent and Well-tolerated**

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Written by Liz Highleyman

HIV © Russell Kightley

The next-generation HIV integrase inhibitor dolutegravir (S/GSK1349572) suppressed HIV viral load as well as efavirenz (Sustiva) but caused fewer side effects in a study of treatment-naïve patients, researchers reported at the 6th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2011) last week in Rome.

Jan van Lunzen from University Medical Center in Hamburg-Eppendorf presented findings from SPRING-1, a multinational Phase 2b trial comparing dolutegravir vs efavirenz as first-line antiretroviral therapy.

Prior studies have shown that dolutegravir (being developed by Shionogi and ViiV Healthcare) can be administered once-daily, unlike the sole approved integrase inhibitor, raltegravir (Isentress), which must be taken twice-daily. Further, dolutegravir does not require a booster, as does another experimental once-daily integrase inhibitor, elvitegravir.

SPRING-1 included 205 patients starting HIV treatment for the first time. The study is designed to last 96 weeks; data from a planned 48-week interim analysis were presented in Rome.

Most participants (86%) were men, more than two-thirds were white, the median age was 37 years, and the mean CD4 count was 324 cells/mm³. About 20% had high baseline viral load (> 10,000 copies/mL).

Participants were randomly assigned to receive 10 mg, 25 mg, or 50 mg dolutegravir, or else 600 mg efavirenz, all once-daily, in combination with either tenofovir/emtricitabine (Truvada) or abacavir/lamivudine (Epzicom).

**Results**

- An unusual 16-week analysis showed that dolutegravir produced rapid HIV suppression, lowering viral load faster than efavirenz.
- At 16 weeks, 90% to 96% of dolutegravir recipients had undetectable viral load (< 50 copies/mL), compared with 58% of efavirenz recipients.
- Participants receiving dolutegravir experienced sustained viral suppression, but efavirenz recipients caught up by week 24.
- The 48-week response rates were 88% to 91% in the dolutegravir arms compared with 82% in the efavirenz arm, not a statistically significant difference.
- An ultrasensitive assay showed that 53% of people taking 50mg dolutegravir and 60% taking efavirenz had viral loads < 2 copies/mL.
There was a trend toward larger CD4 cell gains in the combined dolutegravir arms compared with the efavirenz arm (231 vs 174 cells/mm$^3$), but the difference did not reach statistical significance.

The difference in efficacy was largely driven by the better tolerability of dolutegravir.

Overall, dolutegravir recipients experienced fewer moderate or worse side effects than efavirenz recipients (8% vs 20%, respectively):
- central nervous system or psychiatric symptoms (0% vs 6%, respectively);
- skin rash (0% vs 4%, respectively);
- 2 people taking dolutegravir and 4 people taking efavirenz dropped out due to side effects (1% vs 8%, respectively).

Serious adverse events were also less common in the dolutegravir arm (5% vs 8%, respectively).

No integrase mutations were detected in the 3 participants who experienced virological failure on dolutegravir through week 48 (none of whom were taking the highest dose).

While grade 3 or higher laboratory abnormalities were uncommon, some participants taking dolutegravir experienced small changes in serum creatinine, a potential indicator of impaired kidney function. Changes were noted soon after starting the drug, but they did not progress and there was no difference in glomerular filtration rate (GFR). Van Lunzen explained that dolutegravir appears to inhibit creatinine secretion in the proximal renal tubules.

Looking at blood lipids, there were no notable changes in the dolutegravir arms compared with an increase in total and LDL "bad" cholesterol in the efavirenz arm, leading van Lunzen to describe dolutegravir as "lipid friendly." Triglyceride levels fell among dolutegravir recipients whilst rising among efavirenz recipients.

The 50 mg dolutegravir dose was chosen for further evaluation in Phase 3 studies. The developers are also working on a coformulated single-tablet regimen containing the new drug.

**Reference**

**Drug-Resistant Gonorrhea Case Worries Doctors**
*San Francisco Chronicle*, (07.16.2011) Erin Allday

California health officials are preparing for the eventual arrival of thoroughly drug-resistant gonorrhea following reports of the first-ever case in a sex worker in Japan. Adding to the concern, CDC recently reported increased rates of gonorrhea cases that, though not antibiotic-resistant, are requiring larger doses to treat effectively.

“We’re not seeing any untreatable cases in the United States, but we’re seeing proof that what we’ve been worrying about for a while has actually happened” in Japan, said Dr. Susan Philip, STD prevention director at the San Francisco Public Health Department. “If previous patterns hold true, drug resistance should slowly move its way toward us.”

California and Hawaii are typically the first places in the United States to see drug-resistant strains of infectious diseases, cases that usually arrive from Asia. Immigrants and tourists, traveling west to crowded Asian cities with little health care access, bring new strains back with them, according to epidemiologists.

In December, public health officials began recommending that all gonorrhea cases be treated with two antibiotics — a one-time injection of cephalosporin as well as azithromycin pills. But the larger problem is that the United States has run out of new antibiotics to treat the STD, and they are now needed, said infectious-disease experts.

“We’ll be able to overcome the problem for a while, but eventually the resistance levels will increase and that will become more problematic,” said Stanford University’s Dr. Stanley Deresinski.

“It points to a larger problem we have with antibiotic development,” Deresinski said. “Companies have little incentive to develop new antibiotics, especially for niche markets like gonorrhea. We’re heading into a post-antibiotic age, and it’s pretty scary to think about it.”

**Study: HIV Risks Rise with Some Birth Control**
*Associated Press*, (07.20.2011) Mike Stobbe

Hormone-based contraception was associated with an increased risk of HIV acquisition and transmission in a study presented at the recently concluded 6th International AIDS Society Conference on HIV
Pathogenesis, Treatment and Prevention. The prospective study followed 3,790 heterosexual serodiscordant couples in seven African countries for two years.

One group included nearly 2,500 HIV-infected women, of whom about one-third took hormonal contraception such as daily oral pills or an injectable form at least once, typically in the form of shots taken every few months. If the woman used hormone-based contraception, her uninfected male partner had a 2.61 percent chance of acquiring HIV within a year, compared with a 1.51 percent chance if she did not take such contraception.

In a second group of about 1,300 couples in which the men were HIV-infected but the women were not, about 20 percent of the women took hormonal contraception, mostly shots. The chance of becoming infected was 6.6 percent for women taking hormone-based contraception, compared with 3.8 percent for women who did not.

The study took into account condom use, sexual behavior and other risk factors to rule out alternate reasons for the differences in HIV risk. However, the findings still need to be confirmed in follow-up studies and should not cause women to immediately change birth control practices, the researchers said.

“In many parts of the world, a potential increased risk of HIV would have to be weighed against the consequences of unintended pregnancy, including maternal mortality and poverty, the study authors said. “Contraception is incredibly important to economic and social development of women and children worldwide,” said co-investigator Dr. Jared Baeten of the University of Washington.


Perceived Financial Need and Sexual Risk Behavior Among Urban, Minority Patients Following Sexually Transmitted Infection Diagnosis

According to previous studies, “racial/ethnic and gender disparities in [HIV/STI] may be due in part to factors such a poverty and income-inequality,” wrote the authors, who noted the scarcity of published research on “the effect of the perception of having unmet basic needs on sexual risk behavior.”

Data were collected on perceived financial need and sexual risk as part of a behavioral intervention aimed at promoting STI partner notification and reducing sexual behavior among minority patients presenting for care at one of two STI treatment centers in Brooklyn, N.Y., between January 2002 and December 2004. Data from 528 patients obtained at the six-month follow-up visit were used for the current study.

Among participants, 43 percent were categorized as having unmet needs. These individuals were more likely (62 percent) to report unprotected anal or vaginal sex (UAVI) compared to those who had met needs (53 percent). After controlling for age, sex, site of recruitment, intervention group membership and country of origin, this association was found to be significant: adjusted odds ratio (AOR)=1.28; 95 percent confidence interval (CI)=1.04-1.53.

Stratified analyses found that, in the group that did not receive the intervention, there was a statistically significant interaction between sex and basic needs such that women with unmet needs were more likely to report any UAVI (78 percent) than those with met needs (AOR=1.18; 95 percent CI=1.07-1.24). This relationship was not detected for the men in this sample.

“The significant association between perceived unmet needs and UAVI appears to be particularly relevant for women,” the authors concluded. “These findings provide preliminary evidence that HIV/STI intervention components that seek to directly deal with issues of reduction in partner conflict might be beneficial to women with high perceived unmet basic needs, and for whom a potential dissolution of a relationship may represent a further loss in ability to meet basic needs.”

School Panel to Discuss Distributing Condoms

To help prevent HIV and STD transmission among local students, the City School District (CSD) board policy committee will consider whether to allow community groups to distribute condoms on high school campuses.

The committee is set to meet Tuesday, July 26, at the school district’s central office at 131 W. Broad Street. Although the 5:30 p.m. meeting is open to public attendance, it will be closed to public participation.
The school board has been urged to act on this issue by the Monroe County Department of Public Health and the Metro Council for Teen Potential in response to published data documenting alarming pregnancy and STD rates among Rochester youth. One survey found sexual activity was reported by 58 percent of CSD students in grades 9-12, including 21 percent with at least four partners. And, according to health officials, youths under age 25 comprised nearly 50 percent of area HIV cases reported in 2010.

A forum on STD/HIV interventions in March drew over 100 attendees. Supporters say the statistics justify allowing condom distribution to encourage protected sex. Opponents insist abstinence is the only fool-proof safe sex practice, and that condom distribution engenders promiscuity.

Before any condom distribution could begin in the schools, the committee’s proposal would have to be approved by the school board.

World Leaders Should Either Scale Up Commitment To Polio Eradication Significantly Or Abandon Goal
"There are few ideas as powerful as the eradication of a human disease. But the euphoria around the world’s single success to date – that of smallpox – has led to ever more costly efforts to do the same for polio. World leaders need either to radically step up their commitment or have the courage to abandon the goal explicitly," a Financial Times editorial states.

Eradication "needs a more strategic approach" if it is to succeed, the Financial Times writes. "That means the development and use of improved and differentiated polio vaccines, and their integration into wider childhood vaccination programs. It also means holding more closely to account both the managements of the eradication campaigns, and the political leaders in those countries most affected," the editorial states (7/25).

Catching the West Nile Virus in Action
ScienceDaily (July 25, 2011) — Since 1999, several outbreaks of West Nile Virus, which causes fever or severe neurological symptoms and is transmitted from birds to humans by blood-sucking mosquitoes, have been seen in the U.S., usually during the summer months. But researchers aren’t certain how the virus migrated here—and they don't know how, or where, it will appear next.

Now Prof. Ella Mendelson of Tel Aviv University’s School of Public Health at the Sackler Faculty of Medicine, working with the Israeli Ministries of Health and Environment, has instituted a study that tracks both clinical cases of West Nile Virus and populations of infected mosquitoes. By examining the outbreaks and testing samples of the mosquito populations from high-risk areas (such as those near large bodies of water), her method can identify "danger zones" and produce timely warnings of impending outbreaks. And by providing more information on the dynamics and mobility of the virus, it could also solve the mystery of how the virus migrates.

The research appears in the journal Eurosurveillance.

Don’t forget the repellant
The virus, which was first recorded in the 1930’s and is believed to have originated in Egypt, is now spreading across the globe to non-traditional climates such as Western Europe and North America, says Prof. Mendelson. She and her fellow researchers at the Central Virology Laboratory are geographically tracking the virus, recording where it originates, the genetic types of the virus that are circulated, and the dynamics of infection. They analyze both the occurrences of outbreaks among the human population, as well as the virus' appearance in the mosquito population.

First, mosquitoes are collected from different areas known to be hotbeds of the virus throughout a given country. The females are identified and tested for the presence of the virus, giving researchers information not only on the location of the virus, but the type of the virus as well. In Israel, the information is then relayed to the Ministries of Health and of the Environment so they can keep abreast of the situation and inform the public when necessary. "It’s important to ensure that local authorities take preventative anti-mosquito measures where they can," says Prof. Mendelson.

Keeping the blood banks safe
More recently, says Prof. Mendelson, the researchers have been expanding their interest to include ensuring the safety of donated blood. In connection with the Central Blood Bank in Israel, Prof. Mendelson and her fellow researchers have been testing blood donated to the bank for signs of West Nile Virus.

"We evaluate the blood to see if there is a frequency of donations that might carry the virus," she says, noting that it is important for public health to be involved. A broad approach to West Nile Virus
awareness and safety can be a model for nations which have just begun to contend with outbreaks of the virus in recent years.

When this approach is adopted by other key countries, it will be possible to track West Nile Virus on a global scale. Prof. Mendelson notes that an ounce of prevention is worth a pound of cure. She urges precaution during the evening hours, the mosquitoes’ most active time of day. Wear long sleeves and use plenty of bug repellant, she counsels.

Journal Reference:

Epigenetic 'Memory' Key to Nature Versus Nurture
ScienceDaily (July 25, 2011) — Researchers at the John Innes Centre have made a discovery, reported this evening (24 July) in Nature, that explains how an organism can create a biological memory of some variable condition, such as quality of nutrition or temperature. The discovery explains the mechanism of this memory—a sort of biological switch—and how it can also be inherited by offspring.

The work was led by Professor Martin Howard and Professor Caroline Dean at the John Innes Centre. Professor Dean said "There are quite a few examples that we now know of where the activity of genes can be affected in the long term by environmental factors. And in some cases the environment of an individual can actually affect the biology or physiology of their offspring but there is no change to the genome sequence."

For example, some studies have shown that in families where there was a severe food shortage in the grandparents’ generation, the children and grandchildren have a greater risk of cardiovascular disease and diabetes, which could be explained by epigenetic memory. But until now there hasn’t been a clear mechanism to explain how individuals could develop a “memory” of a variable factor, such as nutrition. The team used the example of how plants “remember” the length of the cold winter period in order to exquisitely time flowering so that pollination, development, seed dispersal and germination can all happen at the appropriate time.

Professor Howard said ”We already knew quite a lot about the genes involved in flowering and it was clear that something goes on in winter that affects the timing of flowering, according to the length of the cold period."

Using a combination of mathematical modelling and experimental analysis the team has uncovered the system by which a key gene called FLC is either completely off or completely on in any one cell and also later in its progeny. They found that the longer the cold period, the higher the proportion of cells that have FLC stably flipped to the off position. This delays flowering and is down to a phenomenon known as epigenetic memory.

Epigenetic memory comes in various guises, but one important form involves histones—the proteins around which DNA is wrapped. Particular chemical modifications can be attached to histones and these modifications can then affect the expression of nearby genes, turning them on or off. These modifications can be inherited by daughter cells, when the cells divide, and if they occur in the cells that form gametes (e.g. sperm in mammals or pollen in plants) then they can also pass on to offspring.

Together with Dr Andrew Angel (also at the John Innes Centre), Professor Howard produced a mathematical model of the FLC system. The model predicted that inside each individual cell, the FLC gene should be either completely activated or completely silenced, with the fraction of cells switching to the silenced state increasing with longer periods of cold.

To provide experimental evidence to back up the model, Dr Jie Song in Prof. Dean’s group used a technique where any cell that had the FLC gene switched on, showed up blue under a microscope. From her observations, it was clear that cells were either completely switched or not switched at all, in agreement with the theory.

Dr Song also showed that the histone proteins near the FLC gene were modified during the cold period, in such a way that would account for the switching off of the gene.

Funding for the project came from BBSRC, the European Research Council, and The Royal Society.

Professor Douglas Kell, Chief Executive, BBSRC said "This work not only gives us insight into a phenomenon that is crucial for future food security—the timing of flowering according to climate variation—but it uncovers an important mechanism that is at play right across biology. This is a great example of where the research that BBSRC funds can provide not only a focus on real life problems, but also a grounding in the fundamental tenets of biology that will underpin the future of the field. It also
demonstrates the value of multidisciplinary working at the interface between biology, physics and mathematics.”

**The First X-ray, 1895**
The discovery of a new and mysterious form of radiation in the late 19th century led to a revolution in medical imaging.

*By Hannah Waters | July 1, 2011*

Wilhelm Röntgen took this radiograph of his wife’s left hand on December 22, 1895, shortly after his discovery of X-rays. National Library of Medicine

At the end of the 19th century, while studying the effects of passing an electrical current through gases at low pressure, German physicist Wilhelm Röntgen accidentally discovered X-rays—highly energetic electromagnetic radiation capable of penetrating most solid objects. His discovery transformed medicine almost overnight. Within a year, the first radiology department opened in a Glasgow hospital, and the department head produced the first pictures of a kidney stone and a penny lodged in a child’s throat.

Shortly after, an American physiologist used X-rays to trace food making its way through the digestive system. The public also embraced the new technology—even carnival barkers touted the wondrous rays that allowed viewing of one’s own skeleton.

Although Röntgen’s lab records were burned at his request when he died, many people have speculated about the sequence of events leading to his discovery. In November 1895, according to one popular account, Röntgen was experimenting with an electron-discharge tube, which he had covered with black cardboard to block the distracting glow caused by electrons striking the tube’s glass walls. To his surprise, he noticed out of the corner of his eye that a fluorescent screen more than a meter away was also glowing. Röntgen dubbed these mysterious rays capable of passing through glass “X” (for unknown) and
subsequently tried to block them with a variety of materials—aluminum, copper, even the walls of his lab—to no avail.

When Röntgen held a piece of lead in front of the electron-discharge tube, it blocked the rays, but he was shocked to see his own flesh glowing around his bones on the fluorescent screen behind his hand. He then placed photographic film between his hand and the screen and captured the world’s first X-ray image. Six weeks later, at the close of 1895, he published his observations and mailed his colleagues a photograph of the bones of his wife’s hand, showing her wedding ring on her fourth finger.

More than 100 years after Röntgen’s first X-ray experiments, Gerrit Kemerink, a medical physicist at the Maastricht University Medical Center in the Netherlands, discovered an X-ray machine from the 1890s very similar to Röntgen’s original and used it to X-ray a hand specimen from his hospital. He found that to acquire the image, the hand received a radiation dose 1,500 times greater than today’s dosage—which explains why many people who were X-rayed or who worked with the original machines suffered from radiation burns and loss of hair. There was also a marked difference in the exposure time required: it took Kemerink 90 minutes to image the hand using the 19th century machine, compared to 20 milliseconds using modern X-ray machines. “How you could keep still, I don’t know!” Kemerink says.

Third of World’s People Infected with Hepatitis—WHO

Reuters, (07.26.2011)

Upwards of 2 billion people—or one-third of the global population—has had hepatitis, World Health Organization experts said at a press conference held Tuesday ahead of the first-ever World Hepatitis Day, July 28. WHO cautions that most infected with hepatitis are unaware and unknowingly passing it on to others through contaminated water and food, blood, semen and other bodily fluids.

“This is a chronic disease across the whole world, but unfortunately there is very little awareness, even among health policy-makers, of its extent,” said WHO hepatitis specialist Steven Wiersma.

WHO has started World Hepatitis Day as a way to bolster public knowledge of the disease and its five primary viruses—A, B, C, D and E—and the “staggering toll” they are wreaking on health care worldwide, said Wiersma. Hepatitis is the leading cause of liver cirrhosis and cancer.

The most prevalent hepatitis virus is B, which may pass from mother to child during labor or in infancy, as well as through unclean needles, said WHO. The E virus, endemic to developing countries, is spread through contaminated water and food.

Although vaccines exist for hepatitis A and B that also may be used to fight D, WHO advises the vaccine for E is scarce, and none exists for C. Programs promoting vaccinations have made strides in several countries, and WHO reports about 180 of its 193 member-states offer the hepatitis B vaccine in infant immunization programs.

However, WHO said testing is paramount to rein in the disease and prevent its spread, in addition to immediately administering quality treatment.

Relationship Characteristics and Contraceptive Use Among Young Adults

Perspectives on Sexual & Reproductive Health Vol. 43; No. 2: doi:10.1363/4311911, (06.01.2011)

Jennifer Manlove, and others

While young adults have high rates of unintended childbearing and STD infection, the authors noted that little research has examined how relationship characteristics affect their contraceptive use. Data from the 2002-05 rounds of the National Longitudinal Survey of Youth yielded a sample of 4,014 dating relationships among sexually active 18- to 26-year-olds. Associations between relationship characteristics and contraceptive use at last sex were assessed by bivariate analysis and multivariate logistic and multinomial logistic regressions.

Use of a contraceptive method at last intercourse was reported in three-quarters of the relationships. A condom only was used in 26 percent of relationships; a hormonal method only was used in 26 percent; and dual methods were used in 23 percent.

When compared with relationships in which first sex occurred within two months of starting to date, those who first had sex before dating were more likely to have used any method at last sex (odds ratio, 1.4), especially condoms or dual methods (relative risk ratio, 1.5 for each). The relative risk of using a hormonal method only, versus no method or condoms alone, grew with relationship duration (1.01) and level of intimacy (1.1-1.2).

“Discussing marriage or cohabitation was associated with reduced odds of having used any method (0.7) and a reduced relative risk of having used condoms alone or dual methods (0.6 for each),” the
authors wrote. “Increasing levels of partner conflict and asymmetry were also linked to reduced odds of any method use (0.97 and 0.90, respectively).

“Prevention programs should address relationship context in contraceptive decision making, perhaps by combining relationship and sex education curricula to foster communication and negotiation skills,” the team concluded.

**Non-Coding RNA Has Role in Inherited Neurological Disorder, and Maybe Other Brain Diseases Too**

ScienceDaily (July 27, 2011) — A team of scientists, led by researchers at the University of California, San Diego School of Medicine, have uncovered a novel mechanism regulating gene expression and transcription linked to Spinocerebellar ataxia 7, an inherited neurological disorder. The discovery promises to have broad ramifications, suggesting that abundant non-coding transcripts of ribonucleic acid (RNA) may be key players in neurological development and function, and could be powerful targets for future clinical therapies.

The research, headed by Albert La Spada, MD, PhD, chief of the division of genetics in the UCSD department of pediatrics, and professor of cellular and molecular medicine, neurosciences and biological sciences, is published in the June 22 issue of the journal *Neuron.*

"Our paper highlights a number of important emerging themes in our understanding of gene regulation in the brain," said La Spada, who is also associate director of the UCSD Institute for Genomic Medicine.

"With the advent of new technologies, science has learned that the vast majority of our transcripts are non-coding," said La Spada. "The challenge going forward is to determine what they do do, and if they have specific functions. It now seems increasingly likely that a multitude of these non-coding RNAs help finely tune transcription regulation in the brain, and perturbation of their work is linked to disease. If we can figure out exactly how, we should be able to gain new insights into how the brain is so precisely regulated—knowledge that may help us better understand how the brain works."

Spinocerebellar ataxia 7 is one of several types of spinocerebellar ataxia (SCA), genetic degenerative disorders characterized by atrophy in the cerebellum of the brain, progressive loss of physical coordination—and in the case of type 7—retinal degeneration that can result in blindness. There is currently no known cure.

Many SCAs are classified as polyglutamine diseases, caused when a protein associated with the disease contains too many repeats of the amino acid glutamine. Polyglutamine diseases are also known as "CAG Triplet Repeat Disorders" because CAG is the sequence of nucleic acids that codes for glutamine.

La Spada and colleagues have long studied SCA. In 2001, they were the first to demonstrate that SCA7 retinal degeneration was the result of transcription dysregulation of ataxin-7, the protein associated with SCA7. Following up, they decided to learn how the gene that expresses ataxin-7 is itself regulated.

The researchers found not one, but two, regulators. The first is called CTCF, a highly conserved protein that regulates a variety of transcriptional processes, most notable establishing insulator domains and controlling genomic imprinting. But they also discovered an adjacent, alternative promoter dubbed intron 2 promoter (P2A) and a transcribed antisense, non-coding RNA, which they labeled SpinoCerebellarAtaxia-AntisenseNoncodingTranscript1 or SCAANT1.

Antisense RNA is single-stranded ribonucleic acid whose primary function appears to be as an inhibitor or suppressor of a gene, though sometimes it can promote gene expression instead. Most antisense RNAs are non-coding, meaning that their sequences do not provide information for making proteins. Even though non-coding RNAs do not provide instructions for the production of vital proteins, they comprise the bulk of the human genome. A major challenge for biomedical research in the 21st century is to figure what they do, and how they do it.

In their *Neuron* paper, La Spada and colleagues highlight one function, at least for SCAANT1. When they investigated how CTCF regulated ataxin-7 gene expression in transgenic mice, they discovered that CTCF promotes the production of SCAANT1 which in turn represses the newly discovered ataxin-7 sense promoter P2A. In mice lacking SCAANT1, sense promoter P2A is de-repressed, allowing a mutant ataxin-7 gene to be expressed, resulting in mice with a version of SCA7. The scientists found a similar lack of antisense SCAANT1 in the fibroblasts and white blood cells taken from human patients with SCA7, implicating deregulation of this pathway in the disease process.
As many inherited neurological disorders are now known to exhibit such overlapping "bidirectional" transcription, the findings in SCA7 could shed light on similar abnormalities with non-coding RNA function in a number of brain diseases.

**Journal Reference:**

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**High levels of unmet need for family planning in people with HIV—couples unaware of conception and contraception options**

Roger Pebody
Published: 26 July 2011

In Kenya, Tanzania and Namibia, just 46% of HIV-positive women and 28% of HIV-positive men have discussed family planning with a healthcare provider, delegates were told at the International AIDS Society conference (IAS 2011) in Rome last week. In these and other African settings, few couples employ dual protection methods (using condoms alongside another contraceptive method), while there is low awareness of strategies which allow a serodiscordant couple to conceive while limiting the risk of sexual HIV transmission.

A number of posters quantified the unmet needs for contraception in various African countries, whilst studies from South Africa and Kenya explored men and women’s feelings about having a child, HIV transmission risk and interventions for safer conception. Treatment-as-prevention and pre-exposure prophylaxis were well accepted, whereas there was scepticism about sperm washing.

The largest quantitative study on unmet needs was conducted in 18 different clinics in Kenya, Tanzania and Namibia, recruiting 1992 women and 1483 men. Participants were living with HIV, sexually active and under the age of 50. The average (median) age of participants was 37, with an average of two children each.

Only a minority of participants reported that they had discussed family planning with a healthcare provider at their HIV clinic. The number who had done so varied from women to men, and from country to country. Overall, 46% of women had had this discussion (68% in Kenya, 40% in Namibia and 32% in Tanzania). The number of men who had had family planning discussions was much lower, at 28% (41% in Kenya, 23% in Namibia and 21% in Tanzania).

Pregnancy was more often desired by men than women. Among men with HIV, 20% hoped for a pregnancy in the next six months, whereas among women with HIV, 14% did. Moreover, 25% of women with HIV believed that their husband or main sexual partner wanted her to become pregnant.

Turning now to those individuals who were not hoping for a pregnancy in the coming months, only a minority were using dual protection, which is widely recommended. Dual protection combines condom use (protective against transmission of HIV and sexually transmitted infections) with another contraceptive method whose effectiveness is not reliant on it being used at the time of sex – for example pills, injections, implants and intrauterine devices.

Only 30% of women who didn’t want to get pregnant reported dual protection. In contrast, 12% used no method at all; 14% reported using a method such as pills or injections; and 44% reported only using condoms.

However, there is such an emphasis on condom use in HIV services that there is a risk that participants exaggerated their use of condoms, in order to tell the researchers what they thought they wanted to hear. The investigators warn that if this is the case, the unmet family planning need is actually greater than they estimate.

Among the men not hoping to get their partner pregnant, 18% reported dual protection; 7% a method such as pills or injections; and 73% condom use only. Again, condom use may be over-reported.

There were variations between countries – for example, Tanzanians were the least likely to report having dual protection.

The researchers conclude that in this group of people with HIV wishing to delay or avoid pregnancy, seven out of ten women and eight out of ten men are not using dual protection and so have unmet family planning needs. It is likely that the limitations of the family planning information provided by healthcare workers is one cause of the low uptake of effective methods.
Qualitative data
To explore attitudes and feelings about conception, researchers in Durban, South Africa, conducted in-depth interviews with 30 women and 20 men living with HIV whose primary partner was either HIV-negative or of unknown status.

As in the previous study, men often had a stronger desire than women to have a child, and women with HIV often felt pressure from their partners to have children. One man explained why he wanted to have a child:

“I think because children are a gift from God. They leave a legacy of the family and they extend and expand your surname so that it won’t die when you die, your legacy won’t perish.”

One woman with HIV said:

“At times he would pretend he was using the condom when he was not. I told him that we should stop thinking about having a baby because I am sick, but he had hope that he will get a child.”

Given the crucial role of men in decisions around pregnancy, the researchers recommend that male partners must be involved in interventions to promote safer conception.

But only a few pregnancies were explicitly planned. One woman said:

“I did want to have a child but I had not really planned which year it would be, but I wanted one... I was the one who wanted a child and I’m the only one who knew that. When I told him [partner] that I was pregnant, he did not have a problem with that.”

Moreover, in these couples, there was considerable confusion over serodiscordancy. Participants found various explanations for why one partner was apparently HIV-negative while the other was HIV-positive. Test results were not always trusted.

“Maybe the virus is hidden but it is there.”

“He then asked me how it happens that he is negative and I am positive and I told him about the window period.”

“I think it’s God’s will that she did not get the virus from me.”

A number of respondents and partners were fatalistic about eventual HIV transmission within the couple. This led to riskier behaviour.

Moreover, some HIV-negative male partners were prepared to risk HIV infection in order to conceive.

“He was the one who took that decision that he wanted another child. I was afraid. I told him that what we are doing is not right because he might get infected. And if he is HIV-positive, he will blame me. He said that if it supposed to happen, then it will happen.”

A few respondents took viral load into account in their decision making.

“After finding out that my viral load was very low, even undetectable, he decided that let’s take a chance and try and see what is going to happen.”

However the majority of respondents were not aware of strategies such as delaying conception until viral load is undetectable and self-insemination.

To further explore strategies for safer conception, another group of researchers interviewed Kenyans who were involved in serodiscordant relationships. They interviewed both the HIV-positive and HIV-negative partners, with the aim of better understanding which techniques would be acceptable to participants.

Some participants were aware of the technique of confining unprotected intercourse to the female partner’s fertile window, and one couple had had a baby with this technique (but had not had tested their child for HIV).

But there was scepticism about sperm washing, with one HIV-positive man commenting:

“It will be so much expensive, the poor people won’t afford it. The psychological part of it – the community – people will view you as getting a child in a scientific way... in such a situation, I think you have to take some legal action because you are not sure that the child who is going to be born is yours. The psychological part of it might haunt you.”

On the other hand, the idea of pre-exposure prophylaxis (PrEP) was well received, with its ease of administration being seen as a major advantage.

“That would be good if there is a pill that can be taken to prevent infection. It would be good.”

Moreover, most respondents responded positively to the idea of antiretroviral treatment of the partner living with HIV, in order to reduce the risk of transmission, although some raised questions about the burden of side-effects when initiating therapy at a high CD4 count.

A recent UK study has also found some ambivalence amongst couples about sperm washing, while the preventative use of antiretroviral therapy was well accepted.
The authors of the Kenyan study conclude that couples attempting conception are highly motivated to consider interventions to reduce their transmission risk. With adequate education, they may be open to the use of HIV treatment, PrEP and timed intercourse.

References

Row over rights of HIV positive foreigners in Botswana’s jails
The government of Botswana has been repeatedly accused of denying ARV drugs to foreign inmates in its prisons.

The country has a policy of universal access to health which means every national has a right to medication.

Botswana became the first country in Africa to distribute the antiretroviral therapy against HIV to those who need it, except foreigners.

This has stoked a debate on prisoners’ rights amongst some politicians and civil society activists.

Lethologile Lucas reports from Gaborone.

SWAZILAND: Desperate HIV-positive people eat cow dung to sustain treatment
MBABANE, 28 July 2011 (PlusNews)—Organizations fighting HIV/AIDS in Swaziland were at first incredulous at reports that hundreds of impoverished HIV-positive rural residents were eating cow dung to give their stomachs something to digest before taking their antiretrovirals (ARVs).

"It seemed too sensational to me when I first heard it, but then an MP stood up in parliament and said it was in his area that people on ARVs were doing this," said Wandile Khoza, an AIDS activist in Swaziland’s central commercial hub Manzini. "It has come to this; the food insecurity most Swazis are experiencing has come up against the world’s highest HIV prevalence rate."

The Swaziland National Network of People Living with HIV/AIDS (SWANNEPHA) confirmed that some of its members were consuming cow dung after MP Josephs Souza of rural Lugongolweni reported first-hand knowledge of the practice following visits to his HIV-positive constituents.

"A rural health motivator took me to one of the patients on ARVs who is among those that now mix cow dung with water and then eat it before taking the tablets," the MP told parliament.

"We have resorted to eating rubbish for purposes of taking our ARVs because they must be consumed after a meal," said SWANNEPHA in a statement.

Research shows that taking ARVs on an empty stomach can exacerbate the side-effects of the drugs, including headaches, dizziness and tremors.

Uncertainty over ARVs
The revelations come as uncertainty over the availability of ARVs prompted Khoza and hundreds of other HIV-positive people to mount an unprecedented protest in Mbabane on 27 July.

Police refused members of SWANNEPHA permission to march in the streets, so 500 members took buses to the Health Ministry to deliver a petition. The umbrella organization also petitioned the National Emergency Response Council on HIV/AIDS (NERCHA), the government unit that finances SWANNEPHA and other AIDS organizations, which is itself facing a funding crisis.

"With the release of the ART budget in ‘dribs and drabs’, any patient on ART would be worried when they are not sure if they will get their monthly stock of treatment," the petition states. "They are human beings who deserve to have peace of mind."

Swaziland is in the midst of a financial crisis that has seen the government cut support to local humanitarian NGOs by 14 percent.

The estimated 65,000 Swazis on ARVs fear that continued budgetary uncertainty could hit their treatment and compromise their survival. One in four Swazis between the ages of 15 and 49 is living with HIV—at 26.1 percent, the world’s highest prevalence—in a population of about one million.

Health Minister Benedict Xaba said on government radio recently that while the government’s financial crisis must concern people living with HIV, there were adequate supplies of ARVs in stock.
AIDS activists are not convinced, however. "The statement that the minister made does not allay fears," the SWANNEPHA petition stated, before accusing the government of misusing state funds and an insincere commitment to the health sector.

The anxiety is partly linked to a recent report in the local media attributed to NERCHA, which claimed that all Swaziland's AIDS prevention programmes had been suspended due to lack of funding. Recent media reports have also caused alarm, with the Swazi Observer carrying a report headlined, "Only Two Months Supply of ARVs Left". A spokesman for SWANNEPHA also noted a contradiction between the Health Ministry's assurances and "the actual facts faced by people on the ground".

**Crisis spreading**

"We have to take on the government-run health system in this country," said SWANNEPHA chairman Patrick Mngometulu. "What good are ARVs if we can't access them because the nurses are on strike and the clinics are closed?"

Political analysts say public sector strikes are inevitable as the government continues to make budget cuts; all ministries have been told to reduce expenditure by 25 percent.

HIV has also hit Swaziland's school system hard. School heads have decided that beginning in August, all public schools will shut down for a month because the government has not fulfilled its commitment to pay fees for all orphans and vulnerable children.

One-fifth of Swaziland's population—an estimated 200,000 children under 15—comprises children orphaned through HIV/AIDS, and head teachers, whose schools rely on student fees and government subsidies, say they can no longer afford to function.

### HHS to study lifting ban on gay blood donors

**July 27, 2011 |**

The Department of Health & Human Services has identified four areas of study to pursue before the regulatory ban on gay men donating blood can be lifted.

In a question-and-answer document requested by Sen. John Kerry (D-Mass.) and Rep. Mike Quigley (D-Ill.) made public Tuesday, the department outlined steps that the Blood, Organ, and Tissue Safety Working Group have identified as necessary before gay and bisexual man are allowed to donate blood. Proposed studies are aimed to address the following four issues:

- how the risk of blood transmissible diseases in the current donor population relate to risk factors in donors;
- the root cause of Quarantine Release Errors, or the accidental release of blood not cleared for use;
- if potential donors correctly understand the current questionnaire and if men who have sex with men would comply with modified deferral criteria; and
- if alternative screening strategy, such as pre- and post-qualifying donation infectious disease testing, for men who have sex with men would assure blood safety while enabling collection of data that could demonstrate safe blood collection.

Under current regulation, men who have had sex with other men since 1977—even once—aren't eligible to donate blood.

Last year, the Advisory Committee on Blood Safety & Availability for HHS voted to recommend that the ban not be changed and cited insufficient scientific data to support revision to the policy. However, the committee also recommended additional research to support a policy allowing low-risk gay and bisexual men to donate blood.

The Q&A prepared by HHS asserts that the department is evaluating these four concerns. To determine the relationship between the risk of transmitting blood diseases with risk factors in donors, HHS has this year instituted a study of baseline data. To determine potential errors in release of blood not cleared for use, HHS plans to hold a public workshop with blood establishments and stakeholders later this year.

"The Department's Blood, Organ, Tissue Senior Executive Council is currently assessing how the above mentioned studies can be supported with limited resources to include long term monitoring through a national hemovigilance program (monitoring or surveillance of the blood supply and blood recipients)," the document states.

As asked whether HHS officials foresee an end to the gay donor ban, HHS doesn’t explicitly say whether the ban will come to end, but that the department is willing to revisit the issue after more information is gathered.
“The Department has worked to develop a plan that will yield scientific data that are currently needed to re-evaluate the policy based on the ACBSA,” HHS states. “When these studies are complete, the Department is committed to a full evidence-based evaluation of the policy. If the data indicate that a change is possible while protecting the blood supply, we will consider a change to the policy.”

In statements, Kerry and Quigley applauded HHS for taking additional steps to lift the ban on gay blood donors.

Kerry said he’s been “working on this a long time in a serious way” and is glad HHS “responded with concrete steps to finally remove this policy from the books.”

“HHS is doing their due-diligence and we plan to stay focused on the end game — a safe blood supply and an end to this discriminatory ban,” Kerry said.

Quigley said the announcement from HHS means “we’re moving in the direction of finally ending this antiquated and discriminatory policy.”

“Sen. Kerry and I will continue to push for a behavior-based screening process both in the name of fairness and a safer blood supply,” Quigley said.

LGBT advocates also praised HHS for taking steps toward allowing gay and bisexual men to donate blood.

Nathan Schaefer, director of public policy at the New York-based Gay Men’s Health Clinic, said he’s “pleased to see” the U.S. government take “critical steps to review outdated blood donation policies.”

“As this research agenda is pursued, GMHC will continue educating the public about the negative consequences of current blood donation policies, and advocating for revised policies that would allow low-risk gay men to donate blood and maintain the highest standard of blood safety,” Schaefer said.

Reflecting a 2006 CDC recommendation that HIV screening be a routine part of health care, Pennsylvania has revised its testing law following two years of intense legislative debate and lobbying.

Beginning Sept. 6, pretest HIV counseling will no longer be mandated, and some test results now given in person can be delivered over the phone. However, the law, signed by Gov. Tom Corbett on July 7, states that “no positive test result shall be revealed ... without affording the ... immediate opportunity for individual, face-to-face counseling” about HIV and other health-related services.

Further, providers can inform patients orally or in writing that HIV testing will be conducted unless they decline or opt out. Currently, patient consent for testing must be in writing. Under the new law, verbal or written consent must be “documented” in the patient’s health record.

“More than half of new infections are transmitted by people who don’t know they’re HIV-positive,” said Dr. Mary van den Berg-Wolf, a Temple University Hospital HIV specialist who lobbied for the changes.

On Wednesday, van den Berg-Wolf and other advocates celebrated the amendment at a meeting with Corbett.

CDC estimates that about one in five Americans who have HIV are unaware of their infection.

Supporters of updating testing laws say treatment can also reduce the risk of HIV transmission; but treatment begins with a positive test result.

10 Million Illegal Drug Users Have Hepatitis C: Study
Agence France Presse, (07.27.2011)
The first study to estimate global hepatitis B and C virus infection rates among injection drug users (IDUs) finds fully two-thirds have been exposed to HCV, while HBV rates vary from country to country.

Australian researchers examined HCV data from 77 countries and HBV data from 59 countries. The HCV infection rate among IDUs ranged from 60 percent to 80 percent in 25 countries, including Spain (80 percent), Norway (76 percent), Germany (75 percent), France (74 percent), the United States (73 percent), China (67 percent), and Canada (64 percent). Twelve nations had infection rates higher than 80 percent, including Italy, the Netherlands, Portugal, Pakistan, and Thailand. In Mexico, 97 percent of IDUs were HCV-infected.

Approximately 80 percent of HCV infections among these IDUs will become chronic, and up to 11 percent will develop cirrhosis within two decades. The health and economic costs of IDU-spread HCV may be as high as or higher than for similarly transmitted HIV cases, the authors said.

HBV rates among IDUs ranged from 5 percent to 10 percent in 21 countries, and exceeded 10 percent in 10 countries, including 12 percent for the United States. Of the countries assessed, Vietnam had the highest rate (20 percent), followed by Estonia (19 percent), Saudi Arabia (18 percent), and Taiwan (17 percent).
In total, some 10 million IDUs worldwide have HCV and 1.2 million have HBV. HBV is the second most-important known cause of cancer, after tobacco. HBV causes some 600,000 deaths annually, said the World Health Organization.

However, unlike HCV, a vaccine against HBV is available. “That is why universal infant vaccination against hepatitis B is so crucial to long-term control of the virus,” said Louisa Degenhardt of the Bernet Institute in Melbourne, and Paul Nelson of the University of New South Wales.

The researchers called on public health officials to increase blood-borne hepatitis prevention efforts and to lower treatment costs. The study, “Global Epidemiology of Hepatitis B and Hepatitis C in People Who Inject Drugs: Results of Systematic Reviews,” was published early online in The Lancet (2011;doi:10.1016/S0140-6736(11)61097-0).

**WHO Marks First-Ever World Hepatitis Day**
The WHO on Thursday marked the first-ever World Hepatitis Day, recognizing a disease that affects nearly one of every three people in the world, the U.N. News Centre reports (7/27). According to a WHO press release, 1.4 million cases of hepatitis A occur each year, two billion people are infected with a hepatitis virus, and at least 130 million people are chronically infected with hepatitis C (7/28).

The WHO is intensifying its campaign against hepatitis B, particularly in the Asia Pacific region, where nine out of 10 countries will not reach a 2012 goal to reduce hepatitis B infections among children, Reuters reports (Lyn, 7/28).

The Lancet on Wednesday published the first worldwide estimates of hepatitis prevalence among people who use injecting drugs, showing that “10 million have hepatitis C while 1.3 million have hepatitis B,” BBC News reports. Compiled by researchers from Australia and the U.S., the figures “show about 67 percent of injecting drug users in the world have been exposed to hepatitis C, while around 10 percent have come into contact with hepatitis B,” according to the news service (7/28).

**U.N. Officials Reiterate Clean Drinking Water And Sanitation Are Human Rights Issues**
One year after the U.N. General Assembly "adopted a resolution declaring that safe and clean drinking water and sanitation is a human right," top U.N. officials on Wednesday "stressed the need to realize the human right to water and sanitation, stating that it is critical not only to a life of dignity but also to achieving progress in the areas such as poverty reduction, boosting child health and combating diseases," the U.N. News Centre reports (7/27). Nearly 900 million people worldwide do not have access to clean water, and more than one million children die each year because of diseases such as cholera that are transmitted by contaminated water, Deutsche Presse-Agentur/M&C notes (Krafczyk, 7/27).

**Niger Facing High Child Malnutrition Rates**
While the world focuses on the famine in East Africa, warnings about high child malnutrition rates in Niger appear "to have gone unnoticed by the international media," AlertNet reports. This year in Niger, 200,000 children between the ages of six months and five years old will require treatment for severe acute malnutrition and 500,000 additional children will need treatment for moderate acute malnutrition, according to Niger officials, AlertNet notes. Though malnutrition rates have decreased recently, "rates remain above international emergency thresholds," the news service writes (Fominyen, 7/27). AlertNet also published a Q&A with Eric Alain Ategbo, UNICEF's nutrition manager in Niger (Fominyen, 7/27).

**Cholera In Congo Has Killed 279, Infected More Than 4,000 People**
"A UNICEF official says a cholera outbreak in Congo has killed 279 people and infected more than 4,000 others in the last four months," the Associated Press/Washington Post reports (7/27). According to the VOA's "Breaking News" blog, "[a] cholera outbreak has been declared in four provinces with northeastern Orientale province showing the most cases." The WHO last week expressed concern that the disease could spread along the Congo River, according to the blog (7/27).

**Gout prevalence swells in US over last 2 decades**
Increase in obesity and hypertension are likely contributors
A new study shows the prevalence of gout in the U.S. has risen over the last twenty years and now affects 8.3 million (4%) Americans. Prevalence of increased uric acid levels (hyperuricemia) also rose, affecting
43.3 million (21%) adults in the U.S. Greater frequency of obesity and hypertension may be associated with the jump in prevalence rates according to the findings now available in *Arthritis & Rheumatism*, a journal published by Wiley-Blackwell on behalf of the American College of Rheumatology (ACR).

Gout, an inflammatory arthritis triggered by crystallization of uric acid within the joints, causes severe pain and swelling. Medical evidence suggests that gout is strongly associated with metabolic syndrome—a group of health conditions characterized by central obesity, insulin resistance, high blood pressure and blood lipid issues—and may lead to heart attack, diabetes and premature death. Prior research found that gout incidence in the U.S. more than doubled from the 1960s to 1990s.

"Our study aim was to determine if the prevalence of gout and hyperuricemia among U.S. adults has continued to climb in the new millennium," said Dr. Hyon Choi, Professor of Medicine in the Section of Rheumatology and the Clinical Epidemiology Unit at Boston University School of Medicine in Massachusetts and senior investigator of the present study.

Researchers analyzed data from the latest U.S. National Health and Nutrition Examination Survey (NHANES) which was conducted in 2007 and 2008, comparing the data with those from previous NHANES surveys (1988-1994). There were 5,707 participants who completed the most recent NHANES survey which included questions regarding history of gout diagnosed by a healthcare professional. Researchers defined hyperuricemia as serum urate level greater than 7.0 mg/dL in men and 5.7 mg/dL in women.

Results from the nationally-representative sample of adult Americans suggest gout and hyperuricemia remain prevalent in the U.S. and compared to earlier NHANES data was 1% and 3% higher, respectively. After adjusting for obesity or hypertension, the differences in prevalence rates were substantially lessened. Further analysis revealed that gout prevalence was higher in men (6%) compared to women (2%); hyperuricemia occurred in 21.2% of men and 21.6% of women.

Dr. Choi concluded, "We found that the prevalences of gout and hyperuricemia continue to be substantial in the U.S. adult population. Improvements in managing modifiable risk factors, such as obesity and hypertension, could help prevent further escalation of gout and hyperuricemia among Americans."


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**In the Pursuit of Dangerous Clumps: Customized Surfaces Help Reveal the Causes of Diseases**

**Press Release — 28.07.2011**

When normal proteins form protein clumps in the body, then alarm bells start ringing. Such clumps, called “amyloids,” are closely associated with Alzheimer’s disease and type 2 diabetes, formerly called adult-onset diabetes. If doctors knew how these proteins form clumps, then they might be able to treat such diseases more efficiently. The physicist Adrian Keller and his colleagues at the Helmholtz-Zentrum Dresden-Rossendorf and the university in Aarhus, Denmark, have succeeded in taking a major step in that direction.

The cell surface assumes a major role in this because the proteins are deposited there and form clumps. In type 2 diabetes and Alzheimer’s, amyloids form on specific cells of the pancreas and the brain, respectively. Even with modern high-performance instruments, it is not possible to observe these processes within the body. Scientists like Adrian Keller, who currently pursues his research at the Interdisciplinary Nanoscience Center “iNano” in Aarhus, are actually attempting to recreate these processes with real proteins on artificial surfaces in the lab.

This sounds easier than it really is. It seems that the formation of these clumps is influenced primarily by the surface’s hydrophilicity and hydrophobicity. Hydrophilic surfaces are easy to wet whereas hydrophobic ones tend to repel water.

Adrian Keller has succeeded in customizing the surface of mica with an apparatus at the Helmholtz-Zentrum Dresden-Rossendorf.
Slow, positively charged atoms of the rare gas argon penetrate only slightly into the crystal surface at low velocity. “This chemically activates the surface without significantly changing the roughness,” explains Adrian Keller the first step of the customization process. Changing the roughness would also have considerable influence on the formation of amyloids.

In the second step, the mica with the activated surface are simply stored in boxes in the lab for several weeks. During this time, the crystal slowly adsorbs hydrocarbons from the air. These turn the initially hydrophilic surface over time into a more hydrophobic surface until after about three months it is completely “water repellent.”

During these three months, Adrian Keller can conduct his experiments and always knows exactly how hydrophobic the mica is at any given moment. He deposits a small protein called “amylin” on the crystal. Specific cells of the pancreas produce this substance together with insulin. If type 2 diabetes develops, the organism initially reacts less well to insulin which regulates the blood sugar level. The pancreas, in turn, produces more insulin and also more amylin. This increases the amylin concentration, and a few amylin proteins suddenly assume a different shape. This process resembles a bit an umbrella turned inside out by a strong gust of wind; thus, creating a sort of “rain bowl.”

The first proteins changed in this manner also influence neighboring proteins and transform additional amylins. The proteins which were turned inside out, in turn, begin to aggregate and amyloids are created. These destroy the surface of some cells and, thus, lower the production of insulin. The organism, in turn, increases the activities of the remaining cells and starts a dangerous cycle which, in the end, can paralyze the entire insulin production.

When the surface in Adrian Keller’s experiments is hydrophilic, then amylin aggregates on the mica into protein clusters which are called “fibrils.” If, however, the surface has aged a few weeks and, thus, becomes more hydrophobic, then tiny clumps are formed which are called “oligomers.” Fibrils and oligomers destroy the cell surface through different mechanisms and, thus, prevent the production of insulin. With the customized surfaces created by the Helmholtz researchers in Dresden, it is now possible for the first time to observe the clumping process of the proteins in detail. One day, strategies might get discovered to prevent the aggregation and, thus, also the development of the disease. And not just for type 2 diabetes, but maybe also for the currently incurable Alzheimer’s disease.

(Text: Roland Knauer)

Publications
Adrian Keller et al., The Journal of Chemical Physics, Vol. 134, Article 104705; DOI: 10.1063/1.3561292 http://jcp.aip.org/resource/1/jcpsa6/v134/i10/p104705_s1

**German E. Coli Code Cracked: Rapid, High-Tech Study of Ongoing Epidemic Creates New Paradigm for Outbreak**

ScienceDaily (July 27, 2011) — A team led by University of Maryland School of Medicine Institute for Genome Sciences researchers has unraveled the genomic code of the *E. coli* bacterium that caused the ongoing deadly outbreak in Germany that began in May 2011.

To date, 53 people have died in the outbreak that has sickened thousand in Germany, Sweden and the U.S. The paper, published July 27 in the *New England Journal of Medicine* (*NEJM*), describes how researchers around the globe worked together to use cutting edge technology to sequence and analyze the genomics of *E. coli* samples from the outbreak as well as closely related strains in a matter of days. They combined those findings with their knowledge of the biology and evolution of the bacteria to learn more about the outbreak. The analysis occurred rapidly enough to inform the physicians treating people who were infected, and assisted epidemiologists as they raced to trace the source of the pathogen.

The research may be the first time that such a comprehensive scientific analysis of an emerging pathogen took place in the first days and weeks of an outbreak, according to the study’s lead author, David
A. Rasko, Ph.D., assistant professor of microbiology and immunology at the University of Maryland School of Medicine, and a research scientist at the Institute for Genome Sciences.

"This technology is evolving extremely rapidly, enabling us to accomplish much more accurate analysis with unprecedented speed," says Dr. Rasko. "It took years and millions of dollars to sequence the first E. coli genome more than a decade ago. Here we are, just months from the start of the German E. coli outbreak, and we've published a paper on it. This paper and the research it describes represent the new paradigm of outbreak investigations."

The researchers collaborated with Pacific Biosciences of California, Inc., a Menlo Park-based company that used its new Single Molecule Real Time technology to sequence the genome of the E. coli strain from the German outbreak. The collaboration also included scientists from the Statens Serum Institute, the World Health Organization Collaborating Centre for Reference and Research on Escherichia coli and Klebsiella in Denmark, as well as Harvard and the University of Virginia.

"The University of Maryland School of Medicine has a global presence spanning 23 countries, and we are proud that our Institute for Genome Sciences has played a leading role in investigating this international health crisis and improving human health worldwide," says E. Albert Reece, M.D., Ph.D., M.B.A., vice president for medical affairs of the University of Maryland and the John Z. and Akiko K. Bowers Distinguished Professor and dean of the School of Medicine.

Dr. Rasko and colleagues at the Institute for Genome Sciences analyzed the genomic data using computational tools, some of which were developed at the Institute. The Institute for Genome Sciences team included postdoctoral researchers Jason Sahl, Ph.D., and Susan Steyert, Ph.D., and lab manager Julia Redmond. Dr. Rasko's expertise is in the molecular pathogenesis and evolution of E. coli, which helped his team to interpret the massive amount of genomic data involved and learn more about the microbe and how it fits into the overall picture of E. coli.

Scientists found that the genome of the German outbreak E. coli strain was mostly enteroaggregative E. coli, a subtype of the bacteria. In carefully examining its genome, they found that the outbreak strain was actually an unusual combination of enteroaggregative E. coli and another subtype, known as enterohemorrhagic E. coli. Researchers also noted that the strain carried a unique set of virulence and antibiotic resistant factors, making it distinct from other strains of the bacteria.

"This is not just a genome paper. It also examines the virulence and biology of the microbe," says Dr. Rasko. "Early in the outbreak, scientists described bacteria as a 'hybrid' strain. This strain is not a true hybrid, because it contains only a small amount of DNA sequence from enterohemorrhagic E. coli. We have not seen these kinds of unique combinations very often in the past. I expect we are going to see them increasingly, now that technology like Pacific Biosciences' has advanced to the point that we can sequence more strains very rapidly and relatively inexpensively."

"The combination of speed, accuracy and cost will lead genomic sequencing to be a diagnostic tool quicker than anyone currently envisages," says Dr. Sahl, the paper's co-author.

When the outbreak began in May, scientists around the world began examining the E. coli strain as soon as samples were available. Many groups were releasing their findings to the public for free—the data in the current study are also publicly available—which resulted in a type of "crowd-sourcing." That is, research was being conducted through the collaboration of a large, disparate group around the globe.

"Usually, science takes place in relative isolation," says Dr. Rasko. "This is the first time we've seen true 'open source' analysis of a microbial genome."

Very early on in the outbreak, German scientists used another sequencing technology and preliminary analysis to determine was unique about the pathogen associated with the outbreak. In fact, they identified a gene that produced a toxin associated with the very symptoms doctors saw in patients, such as severe diarrhea. This gene, known as the Shiga toxin, is produced more when certain antibiotics are used. The findings meant that patients' symptoms would worsen when they were treated with antibiotics. Those initial findings immediately began to inform clinical care, as doctors stopped using antibiotics to treat infected patients. "Our research is a more detailed, comprehensive analysis than that early research," says Dr. Rasko. "This was an international collaboration pulled together in a matter of days. I expect we will see more collaborations like this to deal with new emerging pathogens in the future."

The NEJM paper will provide new, detailed information to assist researchers and physicians as they continue to investigate the ongoing E. coli outbreak in Europe.

"It's exciting to be at the forefront of genomics like this," says Dr. Rasko. "This research was a chance for us to leverage the power of the Institute for Genome Sciences to help create a new paradigm for the study of microbes and outbreaks. It also has implications for genomics as a tool in routine diagnostics."
Identifying Barriers to HIV Testing: Personal and Contextual Factors Associated with Late HIV Testing  
*AIDS Care* Vol. 23; No. 7: P. 892-900, (07..2011) Sandra Schwarcz, and others  
Late diagnosis of HIV, which is associated with increased morbidity, mortality, and health care costs, continues to occur despite the availability of HIV testing. In the current study, researchers accessed the HIV/AIDS case registry of the San Francisco Department of Public Health to identify individuals who developed AIDS within 12 months of their HIV diagnosis; 41 such patients were recruited to participate in qualitative and quantitative interviews.  
Among the participants, 31 were diagnosed with HIV due to symptomatic disease. Fifty percent were diagnosed with HIV and AIDS concurrently. Half the patients had never been tested for HIV prior to diagnosis.  
Barriers to HIV testing included fear (cited most frequently), and being unaware of improved HIV treatment, free/low-cost care and risk for HIV. "Recommendations for health care providers to increase early diagnosis of HIV include routine ascertainment of HIV risk behaviors and testing histories, stronger recommendations for patients to be tested, and incorporating testing into routine medical care," the authors wrote.  
"Public health messages to increase testing include publicizing that (1) effective, tolerable, and low-cost/free care for HIV is readily available; (2) early diagnosis of HIV improves health outcomes; (3) HIV can be transmitted to persons who engage in unprotected oral and insertive anal sex and unprotected receptive anal intercourse without ejaculation and from HIV-infected persons whose infection is well-controlled with antiretroviral therapy; (4) persons who may be infected based upon these behaviors should be tested following exposure; (5) HIV testing information will be kept private; and (6) encouraging friends and family to get HIV tested is beneficial;" the team concluded.  

Ghana Declares Eradication Of Guinea Worm  
Ghana on Thursday declared the eradication of Guinea worm in the country, after a 23-year fight against the disease, the Associated Press/Seattle Times reports.  
"Ghana's triumph over Guinea worm disease serves as a reminder to the world and the remaining endemic countries that the greatest challenges can be overcome with hard work, political commitment, and the support of the international community," former President Jimmy Carter said in a statement from the Atlanta-based Carter Center, which has been working to fight the disease in Ghana since the 1980s, the news agency notes. "Guinea worm disease remains endemic in newly independent South Sudan and in pockets of Mali and Ethiopia. Chad also recently experienced an isolated outbreak," the news agency writes (Kokutse, 7/28).