April 2011 Epidemics and AIDS Update

1. AIDS Virus Blocked From Entering Cells By Engineered Protein Fragment
2. 'Fantastic' data on Novartis' first-in-class hep C antiviral
3. India registers 50 pc dip in new HIV cases: UN
4. HIV+ Prisoners Sue Governor of Alabama
5. First vaccine for viral hepatitis C could become a reality
6. Fratricide of HBV-specific CD8 T cells by NK cells mediated through the TRAIL pathway
7. Soy increases radiation's ability to kill lung cancer cells, study shows
8. Promising Target for AIDS Vaccine
9. HIV Protein Unveils Vaccine Target
10. New H1N1 Mutation Could Allow Virus to Spread More Easily
11. Medicinal Alchemy, circa 1512
12. Disparities: Illness More Prevalent Among Older Gay Adults
14. Major Push to Prevent HIV Infections in Gay Community
15. Bongs Linked to TB by Researchers
16. T cells outpace virus by getting a jump-start on division
17. Search for Advanced Materials Aided by Discovery of Hidden Symmetries in Nature
18. 'Last Resort' Antibiotics Use on the Rise, Study Suggests
19. "Is Parenting Associated with Teenagers'' Early Sexual Risk-Taking, Autonomy and Relationship with Sexual Partners?"
20. Polymerase Inhibitor PSI-7977 Works with Interferon or Companion Drug
21. Cellular Feast or Famine: How Cells Decide Whether They Have Enough Fat
22. Protein Found to Be the Link Missing Between HPV Infection and Cervical Cancer Development
23. Study Looks at Sexual Identity
24. China's HIV/AIDS-Plagued Region Launches Blanket Surveillance
25. FDA Approves Extended-Release Version of HIV Drug
26. America's Role In Developing Country Doctor Shortages
27. Treatment breaks lead to fibrosis in HIV/HCV-co-infected patients
28. China's Health Ministry dismisses "HIV-Negative AIDS" concerns
29. Superbug gene rife in Delhi water supply
30. Climate shifts take health toll on South Africa's HIV infected
31. Effort Seeks to Help Schools Prevent Sex Violence
32. Chinese Ministry, WHO Warn of Antibiotic Overuse
33. Physician Awareness of Sexual Orientation and Preventive Health Recommendations to Men Who Have Sex with Men
35. Monkeys provide malaria reservoir for human disease in Southeast Asia
36. Common Dietary Fat and Intestinal Microbes Linked to Heart Disease
37. HIV Partner Notification Is Effective and Feasible in Sub-Saharan Africa: Opportunities for HIV Treatment and Prevention
38. Periphera Neuropathy Still Common, Capsaicin Patch Can Help
39. Uncommon Resistance Mutations Can Cause First-Line Treatment Failure
40. Cotrimoxazole prophylaxis for HIV-positive infants aids growth, reduces anaemia
41. Young adults who were infected at birth: the complexities of lifelong HIV are increasingly apparent
42. Brain impairment in people with HIV may not be as common as we thought
43. Planned Parenthood, Abortion and the Budget Fight
44. STD/HIV Risk Among Adults in the Primary Care Setting: Are We Adequately Addressing Our Patients' Needs?
45. Cancer burden shifts for people with HIV/AIDS
46. Stress Wrecks Intestinal Bacteria, Could Keep Immune System On Idle
47. Letting There Be More Mosquitoes May Lead to Fewer Malaria Deaths, Say Researchers
48. New Technique Tracks Viral Infections, Aids Development of Antiviral Drugs
49. Big Picture of How Interferon-Induced Genes Launch Antiviral Defenses Revealed
50. Overcoming resistance
51. News in a nutshell
52. The Movement of Goods Around the Cell
53. Of course Africa is ready for PrEP!
AIDS Virus Blocked From Entering Cells By Engineered Protein Fragment

01 Apr 2011

In what could be a potential breakthrough in the battle against AIDS and a major development in the rational design of new drugs, scientists have engineered a new protein that prevents the virus from entering cells. This protein is based on a naturally occurring protein in the body that protects cells from viruses, except the man-made version does not cause inflammation and other side effects at the dosages needed to inhibit AIDS. This discovery was published in the April 2011 issue of The FASEB Journal.

“This is science fiction made reality. These researchers took a protein apart and removed the portion that causes harm, then stabilized and modified the section that has a therapeutic effect,” said Gerald Weissmann, M.D., Editor-in-Chief of The FASEB Journal. “Not only is this good news for people with AIDS, it’s good news for all of us as this research paves the way for similar work for many, many other illnesses.”

The protein fragment is based on a naturally occurring protein called RANTES, which is part of the body’s immune system. RANTES naturally defends the body against HIV/AIDS, but cannot be used as a drug or drug candidate because it has several other biological effects which could cause harmful inflammation. After examining the precise molecular structure of the RANTES protein, the researchers discovered that only a small fragment of the RANTES protein is actually responsible for blocking HIV entry into cells. From there, they dissected the desired section of the RANTES protein and worked to stabilize it without compromising its protective effects. After several sequential steps of molecular refinement and some virtual modeling, the researchers created a peptide with very high potency against HIV, with possible benefits for treating inflammatory diseases such as arthritis and lupus, as well as the prevention of transplant rejection.

“We’re finally able to design smart anti-HIV drugs aimed at the right target. That’s because scientists have spent decades figuring out the molecular details of how the virus enters cells, and the exact chemical structures involved,” Weissmann added. “As the Renaissance sculptors wrought art from crude marble, today’s molecular engineers today use intelligent design to create life-saving chemical masterpieces.”


'Fantastic' data on Novartis' first-in-class hep C antiviral

World News | April 01, 2011

Rhonda Siddall in Berlin

Novartis’ investigational oral agent alisporivir cured almost 50% more previously untreated patients with the most common form of hepatitis C when added to a standard treatment regimen, according to Phase II data presented at the European Association for the Study of the Liver congress in Berlin.

The data were described as “fantastic” by EASL vice secretary Mark Thursz, professor of hepatology at Imperial College, London, while Robert Flisiak from the Medical University of Bialystok, Poland, told the congress: “This novel agent has the potential to be an important component of future hepatitis C treatment.”
The ESSENTIAL study involved 300 previously untreated patients infected with genotype 1 HCV. Of those treated with alisporivir, plus standard of care (pegylated-interferon alfa 2a/ribavirin), 76% achieved superior viral cure compared to 55% of patients on standard care alone 24 weeks after stopping treatment.

The study’s principal investigator, Stefan Zeuzem from Goethe University Hospital in Frankfurt, said: “Hepatitis C is difficult to treat and current therapies are effective only in about half of patients with the most prevalent genotype. These results are exciting because a large majority of patients achieved sustained viral response with alisporivir.”

Alisporivir is the first in a new class of drugs called cyclophilin inhibitors. Unlike other compounds in development that target the hepatitis C virus directly, alisporivir, targets host proteins that the hepatitis C virus uses for replication.

A Phase IIb trial looking at the potential of the agent in HCV patients with genotypes 2 and 3 is underway. The host proteins are needed for replication in all types of HCV infection so there is potential for the agent to have broad activity; there are six variations of HCV.

Phase III trial underway
An international Phase III study is now underway to evaluate the efficacy and safety of alisporivir combined with standard care in previously untreated HCV G1 patients. The Phase II study showed that serious adverse events occurred in 6.9% of patients treated with alisporivir and standard care compared to 5.5% of patients treated with standard care alone. Prof Flisiak reported a higher rate of bilirubin (32.9% versus 1.4% in the alisporivir-treated group compared to standard care alone) but this was transient and reversible and associated with the initial loading dose. Final data from the Phase III ESSENTIAL-2 is expected in March 2013.

Novartis medical director Nikolai Naoumov told Pharma Times World News: “The data is very encouraging because it has produced a significant response in the most common form of HCV which can be very difficult to treat and with a reasonable safety profile. If the results of Phase III and other studies are also encouraging, this agent could offer a paradigm shift in clinical practice by being able to treat a number of genotypes and patients who have not responded to standard care.”

Novartis in-licensed alisporivir, also known as DEB025, from fellow Swiss firm Debiopharm in February 2009.

01/04/2011
India registers 50 pc dip in new HIV cases: UN
New Delhi, Apr 1 (PTI) Good news for the country in combating AIDS as a United Nations report today said India has registered a 50 per cent dip in number of new cases of HIV infections in this decade.

Though the UN remarked the dip in new infections as an "outstanding contribution" in the fight against the disease, it also asked India to do more in containing transmission of HIV from mother to child, an area in which Malaysia and Thailand have done tremendously well among Asian countries.

"In the last decade, India has registered a 50 per cent reduction in the number of new infections. It is an outstanding contribution," Charles Gilks, Country Coordinator (India) of UNAIDS, said at the release of the report here.

According to the report, the number of new infections were 0.24 lakh (24,000) a year 10 years ago while it is 0.12 lakh a year at present.

Every day, the report said, more than 7,000 people are newly infected by HIV, including 1,000 children. AIDS have claimed more than 2.5 crore lives globally and more than six crore people have become infected with HIV in the past 30 years after the disease was detected.

Gilks said the global efforts have got some result as the one is witnessing a reverse trend in spread of AIDS. "The efforts have paid rich dividends. In India alone, four lakh people are on Anti Retroviral Therapy," he said.

However, Peter Piot of London School of Hygiene and Tropical Medicine, cautioned that it was "too premature to cry victory". He said, "we have the tools to fight the disease. But what we lack is a political commitment," he said.

Heidi Larson of London School of Tropical Medicine said steps like decriminalisation of homosexuality in India were a positive step and will have a deep impact on the fight against the disease.

Gilks noted that the disease was becoming more feminised globally with more and more women falling in the high risk category. According to the report, 51 per cent of the affected persons were women.
The report noted that although global HIV incidence is now declining, many countries have failed to satisfy prevention commitments. As a result, it said, the epidemic continues to outpace the response, with two people newly infected for every individual who started ART in 2009.

"With the number of people receiving ART increasing 13-fold from 2004 to 2009, the number of AIDS related deaths declined by 19 per cent during the same period. Still, the epidemic continues to exact severe consequences. From 2005 to 2009, the number of children orphaned by AIDS increased from 1.46 crore to 1.66 crore," it said.

HIV+ Prisoners Sue Governor of Alabama
By Tracey Dalzell Walsh
MONTGOMERY, Ala. (CN) - The ACLU sued Alabama in a federal class action on behalf of HIV-positive inmates, who say they are segregated from the general population in state prisons, and denied training and rehabilitation opportunities, which will hurt their employment prospects when they are released.

The class claims that Alabama is one of only two states - South Carolina is the other one - that routinely segregate HIV prisoners.

"Alabama insists that segregation is justified by the need to provide medical care and to prevent HIV transmission in prison," the complaint states.

But the inmates say, "Prison systems throughout the United States have shown, however, that the states can meet their obligations to incarcerate prisoners safely and to provide them with necessary medical care without requiring prisoners with HIV to forfeit their right to be free from disability-based discrimination."

They say Alabama's policy of segregation in its prisons began in the 1980s, during a "tidal wave of public fear" of the HIV/AIDS epidemic, when "widespread popular confusion existed over the methods of HIV transmission."

All inmates entering the prison system must take an HIV test and "a positive result will determine every aspect of that person's life as long as he or she is in prison. More than the severity of their crime, the length of their sentence, or almost any other factor, the HIV test will determine where the prisoner will be housed, eat and recreate; his or her access to in-prison vocational, rehabilitative, and faith-based programs; and whether he or she will have the opportunity for supervised work in the community," according to the complaint.

At the Limestone prison, "Defendants publicly disclose prisoners' HIV status to all other prisoners, prison staff, and freeworld visitors ... in a variety of ways," the inmates say. "Prisoners with HIV are required to wear white armbands signifying their assignment to the FIIV living area at all times, even when the prisoners are working outside the prison gates. When free-world people take tours of Limestone, correctional officers point out the prisoners with HIV and disclose their HIV status. Some family members have learned that their loved ones have HIV through these various stigmatizing practices. The stigmatization follows the prisoners into the free world, and the widespread knowledge of their medical condition may result in potential employers refusing them jobs."

HIV-positive prisoners in the work release program are not placed in food service jobs and a correctional officer told a female inmate she could not work in a paper company because "she might get a paper cut," according to the complaint.

The plaintiffs say that once they are diagnosed, they are not allowed to eat with fellow inmates, not allowed to work in the kitchen, are denied transfers to jails closer to their homes and they cannot participate in substance abuse programs.

They seek damages under the Americans with Disabilities Act and the Rehabilitation Act due to the practice of "excluding them on the basis of the HIV status from prison programs, jobs, activities and privileges, and publicly disclosing their HIV status." Named as defendants are Gov. Robert Bentley, four wardens and Department of Corrections Commissioner Kim Thomas.

The plaintiffs are represented by Allison E. Neal with the American Civil Liberties Union of Alabama in Montgomery.

First vaccine for viral hepatitis C could become a reality
Berlin, Germany, Friday 01 April 2011: Early data from phase I trials of an HCV vaccine presented today at the International Liver CongressTM show encouraging results, with high immunogenicity and good safety profile.1,2
In the first study1, a therapeutic T-cell vaccine, based on novel adenoviral vectors was used on a small population of treatment naive patients with chronic genotype 1 HCV infection. Intra-muscular vaccination was administered 2 or 14 weeks into a 48-week course of treatment with Peg-IFNa2a/ribavirin. 50% of vaccinated patients had CD4+ and CD8+ HCV specific T-cell responses as detected by ELISpot at 2-8 weeks post boost, showing a strong immunogenicity for the vaccine. Local and systemic adverse events to vaccination were mild, with no evidence of liver immunopathology (measured by liver transaminase levels).

The second study2 looked at the potential for a prophylactic vaccine based on similar novel adenoviral vectors technology (replicative-defective human Ad6 and a novel simian AdCh3 vector that encode 1985 amino-acids derived from the NS3-5 region of a genotype-1b strain). 27 healthy volunteers were vaccinated following a double prime, heterologous boost strategy. The vaccine induced polyfunctional CD4+ and CD8+ T cells responses which were maintained up to 52 weeks post prime. Overall vaccination was very well tolerated with mild/moderate local and systemic reactions and no serious adverse advents.

Professor Heiner Wedemeyer, EASL’s Secretary General commented: "Vaccines are an exciting area of research now with the potential to add to the range of treatments available for patients with chronic viral hepatitis. These are early data but results are very encouraging indeed and as experts, we look forward to more scientific evidence being made available to support this new technology as a future treatment option as well as potentially preventing infection."

Previous research and data presented at the International Liver Congress shows that vaccination with adenoviral vectors induced highly potent and durable T-cell responses in healthy human and that similar vectors may prevent chronic infection in animals.3 This is the first time the immunogenicity and safety of vaccination was tested on HCV patients and healthy subjects.

**Fratricide of HBV-specific CD8 T cells by NK cells mediated through the TRAIL pathway**

*Innovation in science*

A new study presented today at the International Liver CongressTM shows a novel pathway where activated natural killer (NK) cells expressing death ligands may excessively down-modulate the antiviral immune response in chronic HBV patients.1

Blocking the TNF-related apoptosis-inducing ligand (TRAIL) pathway partially reconstitutes HBV-specific T cells, suggesting that these cells are vulnerable to NK cell-mediated apoptosis through this death ligand pathway.

NK cells are one of the main effectors of the innate immune response that plays a key role in containing intracellular pathogen infections. However, it has been increasingly recognised that NK cells may also exert a pathogenic and negative regulatory role during chronic disease.

**References:** Peppa, D. et al. Fratricide of HBV-specific CD8 T cells by NK cells mediated through the TRAIL pathway. Abstract presented at The International Liver CongressTM 2011.

**Soy increases radiation’s ability to kill lung cancer cells, study shows**

*Soy isoflavones block cancer cells’ DNA repair mechanisms while protecting normal tissue*

A component in soybeans increases radiation’s ability to kill lung cancer cells, according to a study published in the April issue of the *Journal of Thoracic Oncology*, the official monthly journal of the International Association for the Study of Lung Cancer.

"To improve radiotherapy for lung cancer cells, we are studying the potential of natural non-toxic components of soybeans, called soy isoflavones, to augment the effect of radiation against the tumor cells and at the same time protect normal lung against radiation injury," said Dr. Gilda Hillman, an associate professor in the Department of Radiation Oncology at Wayne State University's School of Medicine and the Karmanos Cancer Institute in Detroit.

"These natural soy isoflavones can sensitize cancer cells to the effects of radiotherapy, by inhibiting survival mechanisms which cancer cells activate to protect themselves," Hillman said. "At the same time, soy isoflavones can also act as antioxidants in normal tissues, which protect them against unintended damage from the radiotherapy. In a recent study, published in the *Journal of Thoracic Oncology*, we demonstrated that soy isoflavones increase killing of cancer cells by radiation via blocking DNA repair mechanisms, which are turned on by the cancer cells to survive the damage caused by radiation."

Human A549 non-small cell lung cancer (NSCLC) cells that were treated with soy isoflavones before radiation showed more DNA damage and less repair activity than cells that received only radiation.
Researchers used a formulation consisting of the three main isoflavones found in soybeans, including genistein, daidzein and glycitein.

Previously, researchers had found that pure genistein demonstrated antitumor activity in human NSCLC cell lines and enhanced the effects of EGFR-tyrosine kinase inhibitors. This study showed that the soy mixture had an even greater antitumor effect than pure genistein. The soy mixture also is consistent with the soy isoflavone pills used in clinical studies, which have been proven to be safe, researchers said.

**Promising Target for AIDS Vaccine**

ScienceDaily (Mar. 31, 2011) — A section of the AIDS virus's protein envelope once considered an improbable target for a vaccine now appears to be one of the most promising, new research by Dana-Farber Cancer Institute scientists indicates.

The section, a twisting strand of protein known as the V3 loop, is an attractive vaccine target because immune system antibodies aimed at the loop may offer protection against multiple genetic subtypes of HIV-1, the virus that causes AIDS. This is a key prerequisite of any AIDS vaccine because the viruses mutate rapidly and by now comprise millions of different strains that are grouped into different genetic subtypes, or "clades." The researchers' findings are published online in the Public Library of Science journal *PLoS One*.

In the study, investigators injected a monoclonal antibody -- a preparation of millions of identical antibodies that fight viral infection -- into Asian monkeys known as macaques. The antibody came from a person infected with a specific clade of HIV-1. The macaques were then exposed to virus of a different clade. Investigators knew the antibody would latch onto a portion of the virus's V3 loop, potentially barring the virus from invading nearby cells, but they didn't know whether it would prevent infection from a separate subtype of the virus.

The results were striking: All of the treated monkeys were protected from infection by the monkey form of HIV-1, known as SHIV. Monkeys exposed to the virus without receiving the monoclonal antibody, by contrast, became heavily infected.

"This is the first time a monoclonal antibody made against an AIDS virus of one clade has provided complete protection against an AIDS virus of a different clade in animal models," said the study's senior author, Ruth Ruprecht, MD, PhD, of Dana-Farber. "Previous studies have shown that such neutralizing antibodies can protect macaques from infection within one clade; but as more clades of the AIDS virus evolve, it has been unclear whether such antibodies could shield across different clades and prevent infection. Now we have an answer."

AIDS vaccines need to be broadly effective, Ruprecht said, offering protection from a range of HIV-1 subtypes anywhere in the world. It is particularly important for such vaccines to shield against clade C, which accounts for almost 60 percent of worldwide AIDS cases and predominates in sub-Saharan Africa, India, and China. In many parts of the world, clade C has combined with clade B, but retains a clade C protein envelope. Ruprecht and her colleagues have showed that the antibody against the V3 loop prevented infection by a clade C virus.

The antibody treatment technique used in the study is unlikely to confer long-term protection against HIV-1 because the infected antibodies do not remain active in the body for very long. The value of the study is that it demonstrates that antibodies directed against the V3 loop of one clade of HIV-1 can create an immune system shield against another clade.

To translate this discovery into a vaccine, researchers need to devise a way to focus the body's immune system responses to the small portion of the V3 loop that is shared by viruses of different clades. The immune system could then generate its own protective antibodies against the virus. One way of accomplishing this may be to create small molecules that represent this special region inside the V3 loop so the immune system can recognize and attack it.

The study's findings represent something of a vindication for the V3 loop as an immune system target, Ruprecht remarked. While scientists have long known that V3 can spark an immune system response to HIV-1, the loop was thought to be a clever "decoy:" the body would produce antibodies that home in on V3, but these would be unable to block infection by slightly different versions of the AIDS virus. The V3 loop has long been known to mutate very rapidly. Viruses with slightly altered protein envelopes would then begin the infection process. The study has shown that a special region of V3 is a prime target, after all.

**Journal Reference:**

HIV Protein Unveils Vaccine Target

ScienceDaily (Mar. 30, 2011) — An international study headed by a UC Davis scientist describes how a component of a potential HIV vaccine opens like a flower, undergoing one of the most dramatic protein rearrangements yet observed in nature. The finding could reveal new targets for vaccines to prevent HIV infection and AIDS. A paper describing the work was published online in the Proceedings of the National Academy of Sciences.

In the new study, researchers from the U.S., Sweden and France explored the structure and behavior of the HIV envelope protein complex, which could potentially serve as a component of a vaccine aimed at eliciting the human immune system to generate antibodies against HIV.

"By opening up these less exposed regions, we might be able to raise more broadly cross-reactive antibodies to HIV," said R. Holland Cheng, professor of molecular and cellular biology at UC Davis and senior author of the study.

HIV infects a type of white blood cell called the CD4 T cell, weakening the immune system and leading to AIDS. HIV attaches to these cells through the envelope protein complex, which is made up of three gp120 proteins and three gp41 proteins, Cheng said.

First, the gp120 protein attaches to a CD4 protein on the victim cell's membrane. Then it uses gp41 to punch a hole through the membrane.

UC Davis graduate student Carlos Moscoso and project scientist Li Xing, working in Cheng's laboratory, used a cryoelectron microscope to study the structure of the complex and how it changes when it is exposed to a piece of the CD4 protein. A cryoelectron microscope derives three-dimensional images of complex protein structures from samples frozen in liquid nitrogen.

They found that when the HIV protein complex attaches to a CD4 protein, it rotates and flattens, exposing more of the gp41 proteins in the middle -- probably allowing the gp41 protein to get closer to the cell membrane so it can lock on.

It also potentially exposes an area of the virus that would be vulnerable to attack by the immune system, Cheng said. If a person were vaccinated and had antibodies to such a protein region, they might be able to stop the virus at the point of invading the CD4 T cell.

The gp120 protein itself varies considerably between strains, so it has been difficult to make an effective vaccine against it. But these hidden protein regions vary less between different strains of HIV, Cheng said.

Cheng's group is part of the HIV Research and Design consortium formed by the National Institutes of Health to pursue new targets for HIV vaccines. In future work, the consortium plans to test potent antibodies from HIV-positive people who have survived without developing AIDS to see if the antibodies recognize the new potential vaccine targets.

The envelope protein complex was prepared by Novartis Diagnostics and Vaccines Inc. of Cambridge, Mass.

Journal Reference:

New H1N1 Mutation Could Allow Virus to Spread More Easily
In the fall of 1917, a new strain of influenza swirled around the globe. At first, it resembled a typical flu epidemic: Most deaths occurred among the elderly, while younger people recovered quickly. However, in the summer of 1918, a deadlier version of the same virus began spreading, with disastrous consequence. In total, the pandemic killed at least 50 million people -- about 3 percent of the world's population at the time.

That two-wave pattern is typical of pandemic flu viruses, which is why many scientists worry that the 2009 H1N1 (“swine”) flu virus might evolve into a deadlier form.

H1N1, first reported in March 2009 in Mexico, contains a mix of human, swine and avian flu genes, which prompted fears that it could prove deadlier than typical seasonal flu viruses. However, the death toll was much lower than initially feared, in large part because the virus turned out to be relatively inefficient at spreading from person to person.

In a new study from MIT, researchers have identified a single mutation in the H1N1 genetic makeup that would allow it to be much more easily transmitted between people. The finding, reported in the March 2 edition of the journal Public Library of Science (PLoS) One, should give the World Health Organization, which tracks influenza evolution, something to watch out for, says Ram Sasisekharan, senior author of the paper.

"There is a constant need to monitor the evolution of these viruses," says Sasisekharan, the Edward Hood Taplin Professor and director of the Harvard-MIT Division of Health Sciences and Technology. Some new H1N1 strains have already emerged, and the key question, Sasisekharan adds, is whether those strains will have greater ability to infect humans.

WHO labs around the world are collecting samples of human and avian flu strains, whose DNA is sequenced and analyzed for potential significant mutations. However, it's difficult, with current technology, to predict how a particular DNA sequence change will alter the structure of influenza proteins, including hemagglutinin (HA), which binds to receptors displayed by cells in the human respiratory tract. Now that this specific HA mutation has been identified as a potentially dangerous one, the WHO should be able to immediately flag any viruses with that mutation, if they appear.

Identifying this mutation is an important step because it is usually very difficult to identify which of the many possible mutations of the HA protein will have any impact on human health, says Qinghua Wang, assistant professor of biochemistry at Baylor College of Medicine. "These are exactly the types of mutations that we need to watch out for in order to safeguard humans from future disastrous flu pandemics," he says.

Pandemic

On June 11, 2009, about three months after the H1N1 virus first appeared, the World Health Organization declared a level 6 pandemic alert (the highest level). Nearly 5,000 H1N1 deaths were reported to the WHO, and more than 400,000 cases were confirmed, though the true number of cases is significantly higher because many countries stopped counting cases after the first few months of the outbreak, according to the WHO.

In July 2009, a team of researchers from MIT, led by Sasisekharan, and the Centers for Disease Control and Prevention reported in the journal Science that the H1N1 virus was much less easily passed from person to person than seasonal flu viruses and earlier pandemic flu viruses such as the second wave of the 1918 strain.

Sasisekharan and CDC senior microbiologist Terrence Tumpey had previously shown that a major factor in flu-virus transmissibility is the structure of the HA protein, which is found on the viral surface. The tightness of fit between HA and the respiratory cell receptor determines how effectively the virus infects a host.

The 2009 H1N1 strain, like the first wave of 1918 (known as the NY18 strain), does not bind efficiently. However, it took only one mutation of the NY18 virus' HA protein to become the much more virulent SC18 strain, which caused the second wave.

Viral evolution

In the new PLoS study, the MIT researchers focused on a segment of the HA protein that they have shown affects its ability to bind to respiratory cells. They created a virus with a single mutation in that region, which replaced the amino acid isoleucine with another amino acid, lysine. That switch greatly increased the HA protein's binding strength. They also found that the new virus spread more rapidly in ferrets, which are commonly used to model human influenza infection.

If such a mutant virus evolved, it could generate a "second wave" like the ones seen in 1918 and in 1957 (known as the "Asian flu"). "If you look at the history, it takes a very small change to these viruses to have a dramatic effect," Sasisekharan says.
The amino acid in question is located in a part of the viral genome prone to mutate frequently, because it is near the so-called antigenic site -- the part of the HA protein that interacts with human antibodies. Antigenic sites tend to evolve rapidly to escape such antibodies, which is why flu vaccine makers have to use new formulas every year. This year’s vaccine included a strain of H1N1, which is still circulating around the world.

**Journal Reference:**

By Cristina Luiggi

**Medicinal Alchemy, circa 1512**

During the Middle Ages, alchemists developed sophisticated ways to tap the medicinal powers of the Earth’s bounty. Depending on the ailment being treated, flowers, herbs, spices, minerals, and animal flesh all potentially held cures, which could be extracted employing methods not unlike those used by modern organic chemists and pharmacologists. *Liber de Arte Distillandi*, published in present day Strasbourg, France, in 1512, is a compilation of centuries of knowledge intended by its author, German surgeon Hieronymus Brunschwig, to serve as a layman’s guide to the preparation of these natural medicines.

*Liber de Arte Distillandi* was a practical manual for medicinal and alchemical distillation by German physician Hieronymous Brunschwig. Courtesy of the *National Library of Medicine*

With detailed instructions, ranging from the right times to collect herbs to the exact specifications for constructing distillation equipment, Brunschwig hoped to make medicinal alchemy accessible to “the common people that dwell far from medicines and physicians and for them that not be able to pay for costly medicines,” he wrote. Most of the equipment he described, such as funnels, round-bottom flasks, and the iron rings to hold them in place, can still be found in chemistry labs today.
Medieval alchemists greatly advanced the ancient technique of distillation, which separates components in a mixture by taking advantage of different boiling points. They constructed complex apparatuses to distill what they considered to be the ultimate cure—strong alcoholic concoctions typically infused with herbs and spices, among other things (such as horse dung), and collectively known as aqua vitae, or “water of life.”

The “wound man” is a common motif in medieval medical texts, meant to instruct surgeons on how to deal with a variety of injuries. In Liber de Arte Distillandi, Brunswig couples the illustration with a list of distillates to be applied to the wounds depicted. The success of these remedies, however, was hit or miss. While some of the associations between specific plant extracts and conditions were based on centuries of tried-and-true observations, others were made using faulty logic. For example, it was thought that if a plant resembles a particular organ, it could be used to treat it.

NYTimes, April 1, 2011

Disparities: Illness More Prevalent Among Older Gay Adults

By Roni Caryn Rabin

Older lesbian, gay and bisexual adults in California are more likely to suffer from chronic physical and mental health problems than their heterosexual counterparts, a new analysis has found. They also are less likely to have live-in partners or adult children who can help care for them.

The research brief was based on data from the California Health Interview Survey gathered in 2003, 2005 and 2007 by the Center for Health Policy Research at the University of California, Los Angeles. Older gay and bisexual men — ages 50 to 70 — reported higher rates of high blood pressure, diabetes and physical disability than similar heterosexual men. Older gay and bisexual men also were 45 percent more likely to report psychological distress and 50 percent more likely to rate their health as fair or poor. In addition, one in five gay men in California was living with H.I.V. infection, the researchers found. Yet half of older gay and bisexual men lived alone, compared with 13.4 percent of older heterosexual men.

Older lesbian and bisexual women experienced similar rates of diabetes and hypertension compared with straight women of their age, but reported significantly more physical disabilities and psychological distress and were 26 percent more likely to say their health was fair or poor.

More than one in four lived alone, compared with only one in five heterosexual women.

Steven P. Wallace, associate director of the U.C.L.A. Center for Health Policy Research and lead author of the brief, said it was important to raise awareness of these disparities. “The gay culture tends to
be youth-driven, and the aging community network doesn’t usually think about gay and lesbian elders,” he said.

**New AIDS Report Sets Zero New Infections Goal**
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**Associated Press, 04.01.2011** Nirmala George

The UN’s latest major AIDS initiative — its third in the past decade — sets an ambitious target of zero new HIV infections and AIDS deaths by 2015. In 2003, the UN called for expanding access to antiretroviral drugs to 3 million people with HIV in developing nations by 2005, with a follow-up goal of universal access by 2010.

However, to achieve the new zero transmissions goal, member states must make progress against the more than 7,000 new HIV infections globally each day, including 1,000 children. The UN reported data that support the aggressive new agenda.

“The number of people newly infected with HIV declined by 19 percent in the decade before December 2009, with at least 33 countries experiencing a decline in HIV incidence of at least 25 percent,” according to the UN Secretary-General’s 2011 Report on AIDS released Friday in New Delhi. However, the number of infections is increasing in Eastern Europe, Central Asia, North Africa and the Middle East and parts of Asia, it noted.

“The world is beginning to see a reversal of the spread of HIV, and investments are beginning to pay off,” said Charles Gilks, head of the UNAIDS program in India. “Globally, infection rates are falling.”

About 6 million people in developing countries have access to antiretroviral therapy, and mother-to-child HIV transmissions are declining, he added.

The UN’s five AIDS targets also include ending discrimination against those with HIV/AIDS; empowering women and girls toward HIV prevention; and achieving universal treatment access.

To read the agenda, visit:

**Major Push to Prevent HIV Infections in Gay Community**
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**The Nation (Bangkok), 03.31.2011** Pongphon Sarnsamak

The government is boosting HIV prevention efforts targeting men who have sex with men in response to data showing an alarming rise in infections among MSM.

Central to the initiative is the installation of condom machines in 188 venues in areas popular with tourists and MSM. The Department of Disease Control (DDC)’s AIDS, TB and STD Bureau is tasked with completing the project by 2012.

“We expect the HIV infection rate among gay men to fall after the condoms become more available and easy to access,” Dr. Pajjit Warachit, permanent secretary for the Public Health Ministry, said at the project’s launch.

Ministry data show roughly one-third of 10,853 new HIV cases last year were among MSM. The ministry said that rate could increase to 50 percent in the next 14 years without intervention.

Kittinun Daramadhaj, president of the Rainbow Sky Association of Thailand, stressed the need for information on correct condom use. “Even though condoms have now become available in many places, education to teach gay men how to use them correctly is still an important thing,” he said. Some use the wrong size; others withdraw the condom improperly after sex, he said.

In addition, the price of condoms should not exceed 1 baht (US 3 cents), said Kittinun. Many young men complain that condoms are too expensive, prompting them to forgo their use. “This is the real situation happening today,” he said.

Dr. Somsak Akarasilp, deputy director-general of DDC, pledged the department will ask for 100 million baht (US $3.3 million) next year for HIV/AIDS prevention, with the majority supporting condom distribution.

**Bongs Linked to TB by Researchers**
*

**Australian Associated Press, 04.01.2011**

On Monday at the Thoracic Society of Australia and New Zealand’s conference in Perth, researchers are presenting a study on the possible link between TB and water pipes used for smoking marijuana.

The study, by Dr. Michael Hayes and Dr. Susan Miles of the Department of General Medicine at Calvary Mater Hospital in Newcastle, focuses on three TB cases in the Hunter-New England area of New
South Wales (NSW). The three young patients were regular or heavy cannabis users, and a fourth person with similar characteristics also has been recently diagnosed with TB, said Hayes.

While the initial cases are not related, the researchers found a high rate of latent TB among people who shared water pipes, or bongs, with the three. More than 30 close contacts of the three patients were positive for latent TB, said Hayes. Persons who shared a water pipe with the active TB patients had a six-fold risk of being positive, he said.

“Smoking marijuana is a cough-provoking activity and it is usually conducted in a confined environment that is conducive to the spread of the organism,” Hayes noted. “While there is no conclusive proof that TB has been spread by bong smoking, there is sufficient reason to suggest an association between this activity and the spread and severity of the disease.”

TB is one of health risks associated with chronic marijuana use, Hayes pointed out. “The other health problems associated with long-term marijuana use are quite clear and well laid out. It does cause lung disease, and heavy use does cause psychiatric problems,” said Hayes, who also is a specialist in the respiratory and sleep unit at NSW’s John Hunter Hospital.

**T cells outpace virus by getting a jump-start on division**

Killer T cells begin to divide en route to virus-infected tissue, allowing them to hit the ground running when they arrive, according to a study published online on April 4 in the *Journal of Experimental Medicine* (www.jem.org).

Cytotoxic (“killer”) T cells (CTL) defend the body against viruses by attacking infected cells. In order to outpace a rapidly replicating virus, CTL must bolster their numbers via cell division. But early cell division is a slow process, requiring nearly a full day for each round of division. Once activated, the CTL still has to travel through the blood to get to the site of infection.

To make every minute count, the CTL gets a jump-start on cell division during its journey, according to Dorian McGavern and colleagues at the National Institutes of Health. During viral brain infection in mice, up to 1/3 of the CTL in the blood had already initiated the division process. Upon arrival in the brain, the CTL finished dividing within minutes of encountering virus-infected cells.


**Search for Advanced Materials Aided by Discovery of Hidden Symmetries in Nature**
ScienceDaily (Apr. 3, 2011) — A new way of understanding the structure of proteins, polymers, minerals, and engineered materials will be published in the May 2011 issue of the journal Nature Materials. The discovery by two Penn State University researchers is a new type of symmetry in the structure of materials, which the researchers say greatly expands the possibilities for discovering or designing materials with desired properties.

The research is expected to have broad relevance in many development efforts involving physical, chemical, biological, or engineering disciplines including, for example, the search for advanced ferroelectric ferromagnet materials for next-generation ultrasound devices and computers. The paper describing the research will be posted early online by the journal on 3 April 2011, prior to its publication in the journal’s May 2011 print edition.

Before the publication of this paper, scientists and engineers had five different types of symmetries to use as tools for understanding the structures of materials whose building blocks are arranged in fairly regular patterns. Four types of symmetries had been known for thousands of years -- called rotation, inversion, rotation inversion, and translation -- and a fifth type -- called time reversal -- had been discovered about 60 years ago. Now, Gopalan and Litvin have added a new, sixth, type, called rotation reversal. As a result, the number of known ways in which the components of such crystalline materials can be combined in symmetrical ways has multiplied from no more than 1,651 before to more than 17,800 now. "We mathematically combined the new rotation-reversal symmetry with the previous five symmetries and now we know that symmetrical groups can form in crystalline materials in a much larger number of ways," said Daniel B. Litvin, distinguished professor of physics, who coauthored the study with Venkatraman Gopalan, professor of materials science and engineering.

The new rotation-reversal symmetry enriches the mathematical language that researchers use to describe a crystalline material's structure and to predict its properties. "Rotation reversal is an absolutely new approach that is different in that it acts on a static component of the material's structure, not on the whole structure all at once," Litvin said. "It is important to look at symmetries in materials because symmetry dictates all natural laws in our physical universe."

The most simple type of symmetry -- rotation symmetry -- is obvious, for example, when a square shape is rotated around its center point: the square shows its symmetrical character by looking exactly the same at four points during the rotation: at 90 degrees, 180 degrees, 270 degrees, and 360 degrees. Gopalan and Litvin say their new rotation-reversal symmetry is obvious, as well, if you know where to look.

The "eureka moment" of the discovery occurred when Gopalan recognized that the simple concept of reversing the direction of a spiral-shaped structure from clockwise to counterclockwise opens the door to a distinctly new type of symmetry. Just as a square shape has the quality of rotation symmetry even when it is not being rotated, Gopalan realized that a spiral shape has the quality of rotation-reversal symmetry even when it is not being physically forced to rotate in the reverse direction. Their further work with this rotation-reversal concept revealed many more structural symmetries than previously had been recognized in materials containing various types of directionally oriented structures. Many important biological molecules, for example, are said to be either "right handed" or "left handed," including DNA, sugars, and proteins.

"We found that rotation-reversal symmetry also exists in paired structures where the partner components lean toward each other, then away from each other in paired patterns symmetrically throughout a material," Gopalan said. These "tilting octahedral" structures are common in a wide variety of crystalline materials, where all the component structures are tightly interconnected by networks of shared atoms. The researchers say it is possible that components of materials with rotation-reversal symmetry could be engineered to function as on/off switches for a variety of novel applications.

The now-much-larger number of possible symmetry groups also is expected to be useful in identifying materials with unusual combinations of properties. "For example, the goal in developing a ferroelectric ferromagnet is to have a material in which the electrical dipoles and the magnetic moments coexist and are coupled in the same material -- that is, a material that allows electrical control of magnetism -- which would be very useful to have in computers," Gopalan said. The addition of rotation-reversal symmetry to
the materials-science toolbox may help researchers to identify and search for structures in materials that could have strong ferroelectric and ferromagnetic properties.

Gopalan and Litvin said a goal of their continuing research is to describe each of the more than 17,800 different combinations of the six symmetry types to give materials scientists a practical new tool for significantly increasing the efficiency and effectiveness in finding novel materials. The team also plans to conduct laboratory experiments that make use of their theoretical work on rotation-reversal symmetry. "We have done some predictions, we will test those predictions experimentally," Litvin said. "We are in the very early stages of implementing the results we have described in our new theory paper." Gopalan said, for example, that he has predicted new forms for optical properties in the commonplace quartz crystals that are used widely in watches and electronic equipment, and that his group now is testing these predictions experimentally.

Journal Reference:
Venkatraman Gopalan, Daniel B. Litvin. Rotation-reversal symmetries in crystals and handed structures. Nature Materials, 2011; DOI: 10.1038/nmat2987

'Last Resort' Antibiotics Use on the Rise, Study Suggests

ScienceDaily (Apr. 3, 2011) — A large, multi-year study of antibiotic use in Veterans Health Administration's acute care facilities demonstrates dramatically increased use of carbapenems, a powerful class of antibiotics, over the last five years. These drugs are often considered the last treatment option for severe infections with multi-drug resistant pathogens. The increased carbapenem use, which has also been described in non-VA facilities in the US, is alarming because carbapenem-resistant bacteria are becoming more common. Overuse of these drugs could weaken their efficacy, threatening their effectiveness against these and other emerging infections.

The study was presented April 3 at the annual meeting of the Society for Healthcare Epidemiology of America (SHEA).

Using barcode medication administration (BCMA) data for antibiotics administered in 110 VA acute care health facilities from 2005-2009, Makoto Jones, MD, and colleagues identified an increasing trend in the use of broad spectrum antibiotics. In the study's five year period, researchers noted a gradual increase in overall antibiotic use, but striking increases in the use of carbapenems (102 percent increase), intravenous vancomycin (79 percent increase), and combinations of penicillin with beta-lactamase-inhibitors (41 percent increase). Fluoroquinolones were the most frequently used drugs across facilities, accounting for 20 percent of all antibiotic use.

"Use of these antibiotics helps the patient receiving the treatment, but has future consequences for innocent bystanders," said Jones. "The more these drugs are used, the more resistance we see." Additionally, the researchers noted that the quantity of antibiotics reported from VA facilities seems to be similar to reported data from non-VA hospitals in the US.

The use of BCMA to collect data of antibiotic use across VA facilities allowed researchers to analyze which antibiotics are given to any patient on any given day. Jones noted that patient-level data permit powerful studies of antibiotic effects that have not been possible to date. Overall, researchers noted that more than half of all patients received at least one dose of any antibiotic during their hospital stay, regardless of presenting condition.

"In this era of multi-drug resistant organisms, clinicians are placed in a difficult situation. As treatment outcomes of many bacterial infections are influenced by the timing of appropriate therapy, the increasing presence of resistant organisms triggers broader use of these powerful antibiotics for proven or suspected infections when treating patients in the hospital" said Steven Gordon, MD, president of SHEA. "Clinicians must always put the patient first in treatment decisions but we must empower effective antibiotic stewardship programs, infection prevention and control efforts, the development of new diagnostic testing to facilitate better treatment decisions as well as support development of new antibiotics"

Among other measures antimicrobial stewardship ensures effective and appropriate use of the medications we have, with a focus on improving patient safety and treatment outcomes while slowing the growth of resistance. Use of individual level data can be used to inform both the basic science and the implementation of antimicrobial stewardship programs.

"Antibiotic use studies in the U.S. are critical to understanding the basic science of how and why resistance is on the rise," said Gordon. "Dr. Jones' study is a clarion call for a need for better diagnostic tools to identify pathogens and resistance as implementation of effective antimicrobial stewardship."
"Is Parenting Associated with Teenagers' Early Sexual Risk-Taking, Autonomy and Relationship with Sexual Partners?"

**Perspectives on Sexual & Reproductive Health Vol. 43; No. 1; doi:10.1363/4303011** (03..2011) Alison Parkes; Marion Henderson; Daniel Wight; Catherine Nixon

The authors noted that while much research has examined the relationship between parenting and teenagers' sexual risk-taking, little is known about whether parenting is associated “with wider aspects of teenagers’ capacity to form satisfying sexual relationships.”

In central Scotland in 2007, self-reported data were collected from 1,854 students (average age, 15.5 years). Associations between parenting processes and sexual outcomes (delayed first intercourse, condom use, and measures reflecting the context or anticipated context of first sex) were examined in multivariate analyses.

The results indicated that parental supportiveness was positively associated with all outcomes (bets, 0.1-0.4). Parental values restricting intercourse were positively associated with all outcomes except condom use (0.1-0.5). Parental monitoring was found to be associated only with delayed intercourse (0.2) and condom use (0.2). Parents’ rules about TV content were associated with delayed intercourse (0.7) and anticipating sex in a relationship, rather than casually (0.8). “Frequency of parental communication about sex and parental values endorsing contraceptive use were negatively associated with teenagers’ delayed intercourse (-0.5 and -0.3, respectively), and parents’ contraceptive values were negatively associated with teenagers’ expecting sex in a relationship (-0.5),” the authors wrote. The associations were partly mediated by teens’ attitudes, including the value placed on having sex within a relationship.

“Parents may develop teenagers’ capacity for positive and safe early sex by promoting skills and values that build autonomy and encourage sex only within a relationship,” the authors concluded. “Interventions should promote supportive parenting and transmission of values, avoid mixed messages about abstinence and contraception, and acknowledge that teenagers may learn more indirectly than directly from parents about sex.”

**Polymerase Inhibitor PSI-7977 Works with Interferon or Companion Drug**

**SUMMARY:** Almost all treatment-naive hepatitis C patients treated with Pharmasset’s candidate PSI-7977 plus pegylated interferon/ribavirin experienced 12-week sustained response, and more than 90% treated with a PSI-7977 + PSI-938 all-oral combo had undetectable HCV at 14 days, researchers reported at EASL.

**By Liz Highleyman**

Pharmasset is working on a pair of complementary hepatitis C virus (HCV) nucleotide polymerase inhibitors that were designed to work together, PSI-7977 (a pyrimidine analog) and PSI-938 (a purine analog). In preclinical studies the drugs showed promising antiviral activity when combined with pegylated interferon/ribavirin, a non-nucleoside polymerase inhibitor, or each other.

At the European Association for the Study of the Liver’s International Liver Congress (EASL 2011) last week in Berlin, 3 research teams presented data on PSI-7977. Two analyses from the Phase 2b PROTON study looked at PSI-7977 used in combination with standard therapy (pegylated interferon/ribavirin) in people with HCV genotype 1 and in those with genotypes 2 or 3. The third presentation showed early results from a study of PSI-7977 + PSI-938 in various combinations taken for 2 weeks.

**PSI-7977 Genotype 1**

The first PROTON analysis included 121 treatment-naive chronic hepatitis C patients with hard-to-treat HCV genotype 1. About 80% were white and the median age was around 50 years, but the proportion of men varied from 45% to 73% in different study arms. About 40% had the favorable CC IL28B gene pattern, which is associated with better response to interferon.

Participants were randomly assigned to receive PSI-7977 at doses of either 200 mg or 400 mg once-daily, or else placebo, in combination with standard doses of pegylated interferon and ribavirin for 12 weeks. At that point, people who started on triple therapy and experienced rapid virological response (RVR), or undetectable HCV RNA at week 4, took pegylated interferon/ribavirin for an additional 12 weeks; those without RVR continued on pegylated interferon/ribavirin for 36 weeks (thereby reaching the standard duration of 48 weeks).

All but 1 participant in both PSI-7977 dose arms had undetectable HCV viral load (< 15 IU/mL) at week 4. At week 12, 100% in the 200 mg arm and 92% in the 400 mg arm were undetectable (compared with about 60% in the standard therapy arm). No viral breakthrough occurred in any patient who stayed on treatment through week 12. Taken together, 95% of participants who received either dose of PSI-7977 had undetectable HCV from week 4 to 12. Viral load declines did not differ according to IL28B status.
Overall, there were no significant differences in adverse events between participants who received the PSI-7977 combination and those on standard therapy. A total of 4 patients discontinued treatment prior to 12 weeks, 3 of them due to adverse events considered unrelated to PSI-7977. None discontinued due to drug-related adverse events and there were no dose-related blood, liver, or kidney toxicities.

These findings led the researchers to conclude, "High on-treatment response, lack of viral breakthrough, and a promising safety profile support continued exploration of PSI-7977 with abbreviated interferon duration and/or other [direct-acting antivirals] in patients with all HCV genotypes."

**PSI-7977 Genotype 2 or 3**
The second PROTON analysis looked at 25 treatment-naive patients with HCV genotypes 2 or 3. About two-thirds were men, the median age was 47, and 28% had the favorable CC IL28B pattern.

This portion of the study was open-label and all participants received 400 mg PSI-7977 in combination with pegylated interferon/ribavirin for 12 weeks. It also had longer follow-up at the time of presentation, enabling researchers to report sustained virological response rates 12 weeks after completion of therapy, or SVR-12.

One participant was lost to follow-up after the first day. All of the 24 remaining patients experienced RVR and complete early virological response (cEVR), which in this case was also an end-of-treatment response. In an intent-to-treat analysis, 96% of patients achieved SVR-12 -- or 100% if counting only those who stayed in the study. Since everyone responded, it was not possible to analyze what baseline factors contributed to good response.

Again, PSI-7977 was generally well-tolerated. Side effects were uncommon overall, and there were no serious adverse events or discontinuations due to drug-related adverse events.

This research team conclude that the drug’s "[f]avorable risk:benefit [ratio] supports studies in patients with advance disease and broad HCV genotype distribution."

**PSI-7977 + PSI-938**
Finally, the NUCLEAR study tested a combination of PSI-7977 + PSI-938 over 14 days, looking at safety, pharmacokinetics, antiviral activity, and interactions between the 2 drugs.

A total of 40 treatment-naive chronic hepatitis C patients with HCV genotype 1 were allocated into 4 cohorts (each with 8 receiving active drug and 2 receiving placebo). Most were men and the median age was about 45 years.

Cohort 1 received 300 mg once-daily PSI-938 for the full 14 days. Cohort 2 received 300 mg once-daily PSI-938 for 7 days, followed by the combination during the second week. Cohort 3 did the opposite, taking 400 mg once-daily PSI-7977 during the first week and the combination during the second week. Cohort 4 took the same doses of both drugs for the entire 2-week period.

HCV viral load declined rapidly in all treatment arms. Some individuals reached undetectable viral load in as few as 3 days. In all arms, HCV RNA fell by about 4.5 logs by the end of week 1 and by about 5.0 logs by the end of week 2. By the end of the study period 50% of participants in cohort 1, 100% in cohort 2, and 88% in both cohort 3 and 4 achieved undetectable HCV RNA. Taken together, 92% of patients who received any combination of the PSI-938 + PSI-7977 fell below the limit of detection.

Both drugs, and the combination, were generally safe and well-tolerated. Five adverse events, all mild, were considered possibly related to study drugs. There were no serious adverse events, clinically significant laboratory abnormalities, or drug discontinuations for any reason.

"PSI-938 + PSI-7977 is the first purine + pyrimidine combination explored in HCV," the investigators stated. "Monotherapy with either nucleotide analog provided profound antiviral responses rivaling the best antiviral responses reported by combinations employing 2 or more [direct-acting antivirals]."

"Data support progression to a Phase 2 combination study including PSI-938 and PSI-7977," they concluded.

On March 30 Pharmasset announced that it has started enrollment for the ATOMIC study, a Phase 2b trial in which previously untreated patients with HCV genotypes 1, 4, 5, or 6 will receive 400 mg once-daily PSI-7977 in combination with pegylated interferon/ribavirin for 12 or 24 weeks.

In addition, the NUCLEAR investigators noted that another Phase 2 study enrolling people with all HCV genotypes will explore different durations of the PSI-7977 + PSI-938 pyrimidine/purine combination.

4/5/11

**References**


**Cellular Feast or Famine: How Cells Decide Whether They Have Enough Fat**

ScienceDaily (Apr. 5, 2011) — Not all cholesterol is bad. Every cell requires it for growth -- they either have to get cholesterol somewhere or they die. In a new study published April 6 in the journal *Cell Metabolism*, researchers from Sanford-Burnham Medical Research Institute (Sanford-Burnham) and their collaborators found that a protein sensor known to balance cholesterol sources can also access a previously under-appreciated cellular fat storage depot.

The sensor, called sterol regulatory element-binding protein 2 (SREBP-2), monitors cellular cholesterol levels and responds to low levels by switching on genes that allow the cell to either 1) take up more from the bloodstream or 2) manufacture more from cholesterol building blocks inside the cell. Now, Sanford-Burnham's Timothy Osborne, Ph.D., and his team have uncovered a third cholesterol source also controlled by SREBP-2: fat droplets stored inside the cell itself.

"We were searching the mouse liver cell genome to find DNA sequences specifically bound by SREBP-2," said Dr. Osborne, director of the Metabolic Signaling and Disease Program in Sanford-Burnham's Diabetes and Obesity Research Center. "First we were surprised that SREBP-2 binds very close to the genes it regulates -- that's not typical. Second, we were surprised to find that in addition to genes related to fat metabolism and cholesterol balance, SREBP-2 also binds and activates genes responsible for autophagy."

When times get tough, autophagy is the cell's way of recycling its own old or damaged parts. Dr. Osborne and his team found that SREBP-2 uses autophagy as a way to liberate cholesterol stored by some cells in fat droplets. (Here they looked at liver cells, which have large fat droplets. In contrast, other cell types -- neurons, for example -- aren't known to store fat.) When cholesterol was limited, autophagy genes were switched on and fat droplets were joined by autophagosomes (bags of enzymes the cell deploys for self-destruction). As a result, more cholesterol was available for cells to repair membranes, burn as energy or drive other life-sustaining processes.

The role of SREBP-2 in autophagy and cholesterol generation was confirmed using cells engineered to lack the protein. Facing cholesterol shortage, SREBP-2-deficient cells were unable to switch on autophagy genes and autophagosomes did not form as readily as they did in normal cells.

"This study identified a key regulatory step that determines how cells decide whether they have sufficient stored fat, or whether new fat needs to be produced internal cellular sources or obtained from the environment," Dr. Osborne said. "Genetic or environmental conditions that interfere with this regulatory step could lead to diseases such as obesity or cardiovascular disease."

**Journal Reference:**


**Protein Found to Be the Link Missing Between HPV Infection and Cervical Cancer Development**

ScienceDaily (Apr. 5, 2011) — Most women are infected with human papillomavirus (HPV), which can cause cervical cancer -- yet few develop the cancer. Now researchers at Georgetown Lombardi Comprehensive Cancer Center, a part of Georgetown University Medical Center, believe they have found the missing link explaining why: activation of the beta-catenin oncogene.

At the American Association for Cancer Research (AACR) 102nd Annual Meeting 2011, the researchers say that a new mouse model they developed demonstrates that switching the oncogene on in the cervix of HPV infected mice promoted development of aggressive cervical cancer.

These early findings suggest clinical implications that are both preventive and therapeutic, says the study's senior investigator, Aykut Üren, M.D., an associate professor of oncology at Lombardi.

"We can potentially develop a screening method to check for HPV and beta-catenin activation in pap smears," he says. "That will identify individuals at a higher risk of developing cancer compared to ones who are only HPV positive. Then they can be more closely followed for cancer development."
Secondly, Üren points out that there are new drugs being developed to target the Wnt pathway that includes the beta-catenin protein. "Activation of this pathway is very common in colon cancer and is found in a dozen other cancers, so these same novel drugs might be useful in treating advanced stage cervical cancer patients," he says.

Üren points out that while cervical cancer has been kept in check in the U.S. and other developed nations due to use of Pap smears and, of late, the HPV vaccine that protects uninfected females, cervical cancer is the second leading cause of cancer deaths in women worldwide. "New international approaches to control and treat cervical cancer are desperately needed," he says.

Their novel mouse model was created by cross-breeding two other strains of transgenic mice -- one that expresses HPV genes in the cervix and the other that forces the beta catenin/Wnt pathway to be constantly activated, also in the cervix. While the HPV infected mice are programmed to develop cervical cancer, the tumors that grew in the double transgenic mice were larger and more aggressive.

The study was funded by the National Cancer Institute. Gülay Bulut, Ph.D., a postdoctoral researcher in Üren’s laboratory, will present the results at a poster session.

The authors report having no personal financial interests related to the study.

**Study Looks at Sexual Identity**

*Commercial Appeal (Memphis)*, (03.28.2011) Richard Morgan

The recent CDC report on the sexual behaviors of Americans ages 15-44 found that ages 20 to 24 were peaks for both men and women self-reporting a bisexual identity, and troughs for those reporting an exclusively heterosexual identity.

The National Center for Health Statistics’ 2006-08 National Survey of Family Growth included data from 10,404 men and 10,140 women in the 20-to-24 age range. Of women, 6.3 percent identified as bisexual. However, bisexuality was self-reported for just 1.1 percent of women ages 35-44.

The higher their educational attainment, the fewer respondents identified as "something else" — something other than bisexual, heterosexual, homosexual or "did not report." Just one in 100 people with bachelor's degrees self-identified as "something else," compared with one in 10 with a high school diploma or GED.

"College is an opportunity to experiment without judgment, to try on certain roles," said Joel Bumgardner, an associate professor of biomedical engineering at the University of Memphis and faculty adviser to UM’s gay-friendly Stonewall Tigers student group.

"The majority of students here are just like the students in that study," said Tim Smith, 28, an education major who is gay and a Stonewall Tigers member. "We’re just getting away and getting out from the things that might have been holding us back in our hometowns or in our parents’ homes."

With youth culture infused with sexuality, "We’ve seen so much that it’s not a what-is-that mentality,” Smith added. “It’s more: Is that me?”

**China’s HIV/AIDS-Plagued Region Launches Blanket Surveillance**

*Xinhua News Agency*, (03.31.2011)

China's Xinjiang Uygur Autonomous Region sits on a trade route commonly used to transport drugs from the poppy-growing regions of Pakistan and Afghanistan. Needle-sharing among Xinjiang’s drug users has long been blamed for the region’s high incidence of HIV/AIDS. With 33,149 HIV infections reported through the end of last year, Xinjiang accounts for one-tenth of the nation’s total cases.

In response, the Xinjiang health bureau has launched a major new surveillance effort in health care settings. In cities, counties or districts where more than 300 HIV/AIDS cases have been reported, hospitals must administer mandatory HIV tests to all inpatients and to at least 50 percent of outpatients. In areas with more than 500 reported HIV/AIDS cases, hospitals and clinics must conduct mandatory HIV tests of all inpatients and 80 percent of outpatients. The policy was announced March 31.

Yin Yulin, Xinjiang’s top health official, said some parts of the region now have a “high prevalence” of HIV, and it has become “very difficult” to monitor the movements of those with the virus.

“The epidemic has shown a new trend,” Yin said. “While the spread of the virus among intravenous drug users remains hard to rein in, sex has replaced drug-taking as the main channel of Xinjiang’s AIDS prevalence.”

The new blanket surveillance is seen as a way to account for every individual living with HIV/AIDS in the region, health authorities said.
FDA Approves Extended-Release Version of HIV Drug

_Hartford Courant_, (04.04.2011)  Rinker Buck

The Food and Drug Administration has approved an extended-release form of the HIV drug nevirapine. Boehringer Ingelheim Pharmaceuticals’ Viramune XR is a 400 mg tablet taken once daily; the earlier version required twice-daily dosing. “Viramune XR is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults,” FDA said. Patients needing financial assistance to access the drug are asked to telephone 800-556-8317 or visit www.RxHope.com. To read FDA’s statement, visit http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm248800.htm.

America's Role In Developing Country Doctor Shortages

In his column in the _Guardian_, Jonathan Wolff, a professor of philosophy at University College London, says despite the U.S. being viewed as having the best system of higher education in the world, the country "simply does not train enough doctors to meet its voracious appetite for medical attention" and therefore "is compelled to raid the world to make up the difference."

"For decades about 25% of doctors practising in the U.S. received their training elsewhere. This now amounts to close to 200,000 doctors educated abroad. Around 5,000 were trained in sub-Saharan Africa; predominantly Ghana, Nigeria and South Africa, but also elsewhere. In 2002, there were 47 Liberian-trained doctors working in the U.S., and just 72 working in Liberia. And even when a doctor is recruited from Canada, Canada then looks to South Africa, and South Africa to wherever it can. The poorest will always lose out," according to Wolff.

"So while we look with envy at the wealth and achievements of the top American universities, we should bear in mind that not all is as well as it seems. In fact, it may be that the weakness of the U.S. higher education system is contributing to the health and development crisis in some of the world’s poorest regions," he concludes (4/4).

Treatment breaks lead to fibrosis in HIV/HCV-co-infected patients

Michael Carter
Published: 07 April 2011

Interrupting HIV therapy is associated with the progression of liver damage in patients co-infected with HIV and hepatitis C, Canadian investigators report in the online edition of _AIDS._

Taking a break from antiretroviral therapy more than doubled the risk of fibrosis.

“We found a significant, harmful effect of interruption on the development of fibrosis after accounting for clinical factors,” comment the investigators, who call for further research into the reasons co-infected patients take breaks from their HIV treatment.

Liver disease is now a major cause of illness and death in patients co-infected with HIV and hepatitis C. However, some research suggests that treatment with antiretroviral drugs protects co-infected patients from the development of liver disease.

Results of the SMART study showed that interrupting antiretroviral therapy increased the risk of illness and death from HIV and non-HIV-related causes, including liver disease.

Although treatment interruptions are not recommended, they still occur. Canadian investigators hypothesised that breaks from HIV therapy contributed to the development of liver fibrosis in co-infected patients.

To test this theory they designed a prospective study involving 514 patients who were enrolled in the Canadian HIV-HCV Co-infection Cohort (CCC). All the patients were recruited between 2003 and 2009, and none had fibrosis at baseline.

Liver fibrosis was assessed using a blood test that measured aspartate aminotransferase (AST)-to-platelet-ratio (APRI). This is a validated surrogate marker of fibrosis. An APRI score of 1.5 used to diagnose significant fibrosis and cirrhosis was diagnosed if an individual had an APRI score of 2.0 or above

Patients were assessed at baseline and then at six-monthly intervals. Blood samples were taken and patients reported if they had interrupted HIV therapy.

The median duration of follow-up was 1.02 years. During 760 person-years of follow-up, 10% of patients achieved an APRI score of at least 1.5 and 10% interrupted their antiretroviral therapy.
The total number of treatment interruptions was 55, with two patients interrupting their therapy twice. The median duration of each interruption was 180 days. Interruptions peaked in 2004 when 15% of individuals took a break from their HIV treatment.

Overall, only 38% of patients resumed therapy during follow-up.

Platelet count fell by a median of 2x10⁹/l when treatment was interrupted and AST increased by 21 u/l.

Statistical analysis that controlled for potentially confounding factors (including changes in CD4 cell count and viral load) showed that interrupting HIV therapy more than doubled the risk of liver fibrosis (hazard ration [HR] = 2.52; 95% CI, 1.20-5.28). A baseline APRI score of between 0.5-1.49 was also strongly correlated with the progression of liver disease.

Their analysis also showed a treatment interruptions were associated with a non-significant increase in the risk of serious clinical liver disease or cirrhosis (HR = 2.12; 95% CI, 0.87-5.16). The investigators believe that it was only lack of statistical power that prevented this relationship from achieving significance.

" Interruption of antiretroviral therapy has been shown to lead to a greater risk of nonopportunistic disease-related death in randomized trials, particularly among HIV-HCV co-infected participants," comment the investigators.

They believe that the results of their study have for the first time shown that interrupting HIV treatment "was associated with the development of significant liver fibrosis among participants co-infected with HIV and HCV."

A possible reason for the association is the increased inflammation that occurs when treatment is interrupted.

However, the investigators acknowledge that their study has some limitations. Although the APRI score is a validated measure of fibrosis in co-infected patients, it is known that stopping HIV therapy can lead to changes in platelet counts. Nevertheless the investigators had confidence in their findings. Closer analysis of platelet counts and AST scores before and during treatment breaks lead them to conclude that fibrosis did progress when therapy was interrupted.

"Studies to determine factors associated with antiretroviral treatment interruption in co-infected patients would be beneficial to assist clinicians in reducing treatment discontinuations as would studies aimed at understanding the underlying mechanisms driving fibrosis in this setting," conclude the authors.


**China’s Health Ministry dismisses "HIV-Negative AIDS" concerns**

BEIJING, April 6 (Xinhua) -- There is no evidence that the people claimed to have been infected by the so-called "HIV-Negative AIDS" in China are infected by AIDS virus, according to China’s Ministry of Health Wednesday.

Neither are there any clinical, laboratory or epidemiological evidence that these people suffer any infective disease, said Deng Haihua, spokesman of the ministry.

His remarks was made in response to some concerns that some people claimed that they had infected by some AIDS-like virus but were tested to be HIV negative.

The "patients" said they had displayed symptoms very similar with AIDS, such as swollen lymph nodes, subcutaneous bleeding, joint pain, fatigue, nights sweats and emaciation.

From 2009 to 2010, the Chinese Center for Disease Control and Prevention had tested 59 volunteers of the so-called "HIV-Negative AIDS patients", and found no evidence that there were any infection of a new or unknown virus, Deng said.

A recent epidemiological probe conducted in February and March this year among the target "patients" in Beijing, Shanghai, Jiangsu, Zhejiang, Hunan and Guangdong found no sign of infectivity of the symptoms, Deng said.

**Superbug gene rife in Delhi water supply**

Global implications as NDM-1 gene is found to be widespread in water used for cooking, washing and drinking

Sarah Boseley, health editor

*The Guardian*, Thursday 7 April 2011

A gene that causes a wide range of bacteria to become resistant to antibiotics has been found in the water supply in Delhi, with worrying implications for the rest of the globe.
International travel and medical tourism have already brought the gene, known as NDM-1, to the UK. A team of scientists reported last year that they had found NDM-1 positive bacteria in a small number of patients who had visited India for kidney or bone marrow transplants, dialysis, pregnancy care or burns treatment, while others had undergone cosmetic surgery.

A paper by Timothy Walsh from Cardiff University and colleagues, published in the Lancet Infectious Diseases journal, reveals that the gene, known as NDM-1, is widespread in the water used for cooking, washing and drinking in Delhi. It will inevitably be brought into hospitals in the gut flora of patients. The potential for movement around the world is high.

NDM-1 can cause many types of bacteria – including E coli and Klebsiella pneumoniae – to become resistant to powerful antibiotics called carbapenems, which are used when other antibiotics fail to work. The team also found the gene had spread to bacteria that cause cholera and dysentery. "Worryingly, dysentery caused by this particular isolate is currently untreatable," said Mark Toleman, one of the authors.

The findings are published on World Health Day, which this year is dedicated to preserving the healing powers of the antibiotics we still have. The World Health Organisation warns that more than 25,000 people die every year in the EU alone from infections caused by antibiotic-resistant bacteria.

"We need to raise the alert that we are at a critical point where antibiotic resistance is reaching unprecedented levels and new antibiotics are not going to arrive quickly enough," said Zsuzsanna Jakab, WHO regional director for Europe.

She said antibiotics were being taken for granted and overused. "There are now superbugs that do not respond to any drug. Given the growth of travel and trade in Europe and across the world, people should be aware that until all countries tackle this, no country alone can be safe."

There are few new antibiotics in the pharmaceutical pipeline, because they have proved hard to discover and are not lucrative investments for drug companies – new drugs would be kept as a last resort and used very infrequently to begin with.

The scientists involved in the study in New Delhi took samples both from tap water and seepage water collected in pools in streets or in rivulets. The NDM-1 gene was found in two of 50 drinking water samples and 51 of 171 seepage samples.

Poor sanitation in India, where 650 million people do not have access to a flush toilet and probably not to clean water either, is a major issue in the spread of bacteria carrying the gene. High temperatures, which are important for NDM-1 mobility, a crowded population, massive antibiotic over-use, under-use and misuse and poor infection control also contribute.

The situation is made worse by the government’s refusal to accept the problem, said Toleman. "Following the publication of this study, the Indian government took draconian measures against the Indian scientists who collaborated with us and our colleagues were threatened," said Toleman.

"This had the effect of severing these productive collaborations and the Indian authorities were in denial of the massive problems southern Asia is facing."

But he added that he thought India was "starting to come out of denial". It has now taken steps towards introducing a surveillance programme. "That's a massive step in the right direction," he said.

Climate shifts take health toll on South Africa's HIV infected

07 Apr 2011 13:06
HLABISA, South Africa (AlertNet) - Since HIV/AIDS left her husband bedridden and weak, the burden of putting food on the table has fallen solely on Thombizodwa Maseko's shoulders.

Waking early every morning, she walks five kilometers to fetch fuel, firewood and water before spending some time tending to her small plot of land in Hlabisa in South Africa's KwaZulu-Natal province.

She cultivates by hand. There are no tractors, oxen or ploughs to help work the field that is the main source of food for Maseko, her husband and their six children.

As if life wasn't hard enough, Maseko is worried about her crops - every year they receive less and less rain.

"At times I feel God is unfair," she says as she finishes dressing her 4-year-old son for school. "I have become the father and mother of this house, feeding and taking care of my sick husband. The rains are no longer coming the way they used to 10 years ago. We are harvesting nothing."
Normal annual rainfall for Hlabisa, one of KwaZulu-Natal’s poorest areas, is 766 mm, but over the past few years the area has been receiving less than half that amount, according to the South African Weather Service.

A long rainless stretch this year has underscored the urgency of water problems in a region that used to produce much of the country’s corn, livestock and cotton.

"I tried to grow some crops this season, but this is what we have," Maseko says pointing to a plot carved out of a rocky hillside, where clumps of maize grow only knee high.

"I think I’m going to lose all my harvest this year. If we don’t get rain before May, I won’t be able to harvest anything," she said.

Climate change is making life particularly hard for southern African communities dealing with poverty, high rates of HIV/AIDS and now increasingly extreme weather that threatens food supplies.

Unreliable harvests often means less food to go around and lower levels of nutrition, a threat to families like Maseko’s because nutritious food is key to keeping HIV-positive people healthy as long as possible.

Scientists say climate shifts now underway are likely to bring about more extreme weather around the world, including worsening droughts, floods and storms.

Many of those problems have both direct and indirect impacts on health. Besides affecting harvests and nutrition, a warming climate allows mosquitoes and other disease-transmitting insects to move to new locations, bringing with them diseases such as malaria and dengue fever, experts say.

**Health Impact**

According to the South African Department of Health, Hlabisa has seen more frequent outbreaks of malaria in recent years. Deaths from the disease rose to 423 last year in South Africa compared with 14 in 1992.

Dr Constansia Musvoto, a researcher at the Council for Scientific and Industrial Research (CSIR), says South Africa has become warmer by 0.7 degrees Celsius over the past century, increasing the amount of the country vulnerable to malaria. Mosquitoes that carry the parasite thrive in warmer climates and cannot survive in temperatures below 15 degrees Celsius.

Under current climate change projections, "temperatures will increase by up to 6 degrees Celsius, while rainfall will drop by as much as 40 percent in some parts of the region (in the next 50 years). Due to rising temperatures, malaria will spread more widely," Musvoto predicted.

Malaria is not the only threat. Lower crop yields due to changing weather patterns may result in malnutrition and under-nutrition for those depending on subsistence farming, experts say.

A lack of fresh water could lead to increasing rates of diarrhoeal disease such as cholera and dysentery.

At greatest risk are the most weakened and vulnerable, such as Maseko’s husband, one of at least 5.7 million people infected with HIV in South Africa.

With a population of 50 million, South Africa has one of the world’s highest Human Immunodeficiency Virus (HIV) infection rates. As many as 1,000 people die every day of AIDS-related illnesses.

Standing at the door of her small hut hidden deep in the swaying grass, with her husband lying coughing inside, Maseko talks of the threat posed by changing weather patterns and HIV/AIDS.

She says a combination of unpredictable weather and a high prevalence of HIV/AIDS means agricultural skills and know-how have been lost. Fewer people are now able to work the land, particularly as they must care for sick relatives or are ailing themselves.

Families like Maseko’s are losing income in a district which is already one of the most deprived.

Only 13 percent of the people in the district are formally employed according to the municipality’s 2010 Integrated Development Plan. More than 60 percent of the households use water from unprotected springs, dams, stagnant pools and rivers.

Over 47 percent of the households do not have any form of sanitation service, and 77.4 percent have no electricity for heating.

Many women in the community are caring for their sick husbands, reducing the time they can devote to their children and to planting, harvesting and marketing crops. When their husbands die, they are often stripped of credit and land rights in a cycle of vulnerability, and some eventually die themselves of HIV/AIDS, contracted from their husbands.
**Effort Seeks to Help Schools Prevent Sex Violence**

*Associated Press*, (04.04.2011) Kathy Matheson

Vice President Joe Biden and Education Secretary Arne Duncan are helping launch an awareness campaign aimed at stopping school-based sexual violence.

“Students across the country deserve the safest possible environment in which to learn. That’s why we’re taking new steps to help our nation’s schools, universities and colleges end the cycle of sexual violence on campus,” Biden said ahead of the campaign’s debut at the University of New Hampshire-Durham on Monday.

Schools will receive letters and brief outlines of their responsibilities under Title IX, which bans sexual discrimination, harassment and violence.

Last year, the Education Department’s Office of Civil Rights received 35 complaints of sexual violence, about two dozen of them at the K-12 level. Department data also show that roughly 20 percent of college females will be victims of an attempted or actual sexual assault, as will about 6 percent of undergraduate males. “Every school would like to believe it is immune from sexual violence, but the facts suggest otherwise,” said Duncan.

New Hampshire was selected due to its best practices in educating, preventing and responding to sexual assaults, say officials. The university created the “Bringing in the Bystander” program, which teaches passers-by to safely and effectively intervene to stop such attacks. Other universities have since adopted the program. In addition, the school was one of the first to fund an on-campus crisis center for rape and sexual harassment in 1988, said spokesperson Erika Mantz.

**Chinese Ministry, WHO Warn of Antibiotic Overuse**

*Associated Press*, (04.07.2011) Gillian Wong

Action is needed now to halt the growth of drug-resistant forms of TB and other diseases in China, representatives from the Ministry of Health and the World Health Organization (WHO) warned today. Marking World Health Day in Beijing, the officials said overuse of antibiotics is the primary cause of drug-resistant disease strains.

Approximately 6.8 percent of TB cases in China are multidrug-resistant, compared to 2 percent in most developed countries, said Dr. Michael O’Leary, WHO’s China representative. Worldwide, roughly 440,000 new MDR TB cases emerge annually, killing at least 150,000 people, said WHO.

“Infections caused by resistant microorganisms often fail to respond to conventional treatment, resulting in prolonged illness and greater risk of death,” said O’Leary. New drugs cannot be developed fast enough to replace those that have lost their effectiveness, and that is why the problem needs immediate attention, he said.

Antibiotic overuse is very common in China, since it is a way for hospitals to boost their bottom lines. Vice Health Minister Ma Xiaowei urged hospitals to use the drugs in “scientific and rational” ways.

Furthermore, antibiotics are being misused by the food industry. Some 50 percent of antibiotics used globally are given to animals raised for food, said Dr. Fabiola Scano, a WHO medical officer with the TB program in China. The drugs show up in diverse parts of the food supply, from farmed fish to honey. Evidence indicates “the more antibiotics are used, the higher is the antibiotic resistance in humans,” Scano said.


**Physician Awareness of Sexual Orientation and Preventive Health Recommendations to Men Who Have Sex with Men**

*Sexually Transmitted Diseases Vol. 38; No. 1: P. 63-67*, (01.2011) Andrew E. Petroll; Katie E. Mosack

Because men who have sex with men have unique health needs and risks, providers who assume their patients are heterosexual may be offering suboptimal care to their MSM patients. The authors of the current study set out to describe primary care providers’ knowledge of their patients’ sexual orientation and the demographic and provider-related characteristics associated with this knowledge; and to determine whether PCP knowledge of patients’ sexual orientation was associated with making appropriate recommendations for preventive and diagnostic care.

A cross-sectional survey was completed by 271 MSM. The researchers measured MSM’s disclosure of their sexual orientation and demographic information, and they noted the PCPs’ recommendations for preventive care.
Seventy-two percent of participants said their PCP knew their sexual orientation. Disclosure was more likely for MSM whose PCP was female, gay and/or younger. MSM who were black, from rural areas and earned less than $15,000 a year were less likely to have disclosed. PCPs who knew the sexual orientation of their MSM patients were more likely to recommend HIV testing (59 percent vs. 13 percent) and hepatitis A or B vaccination (32 percent vs. 16 percent). Inconsistencies were noted between participants’ self-reports of risk behaviors and PCP recommendations.

“Disclosure of sexual orientation is associated with several patient-related and provider-related characteristics,” the authors concluded. “Lack of disclosure to providers significantly decreased the likelihood that appropriate health services were recommended to participants. Efforts to promote discussion of sexual orientation within the primary health care setting should be directed toward both PCPs and MSM.”


SUMMARY: New U.N. report finds that HIV infection have fallen by more than 25% in over 30 countries and more than 6 million people worldwide are on antiretroviral treatment, but much remains to be done.

Below is a the edited text of a press release issued by the U.N. describing the report and its findings. The full report is available online at www.unaids.org.

UN Secretary-General Outlines New Recommendations to Reach 2015 Goals for AIDS Response

In lead-up to June High Level Meeting, progress report presents overview of efforts needed to help countries achieve universal access to HIV services and zero new HIV infections, discrimination and AIDS-related deaths

Nairobi -- March 31, 2011 -- Thirty years into the AIDS epidemic, investments in the AIDS response are yielding results, according to a new report released today by United Nations Secretary-General Ban Ki-moon. Titled “Uniting for universal access: towards zero new HIV infections, zero discrimination and zero AIDS-related deaths,” the report highlights that the global rate of new HIV infections is declining, treatment access is expanding and the world has made significant strides in reducing HIV transmission from mother to child.

Between 2001 and 2009, the rate of new HIV infections in 33 countries --including 22 in sub-Saharan Africa-- fell by at least 25%. By the end of 2010, more than 6 million people were on antiretroviral treatment in low- and middle-income countries. And for the first time, in 2009, global coverage of services to prevent mother-to-child transmission of HIV exceeded 50%.

But despite the recent achievements, the report underscores that the gains are fragile. For every person who starts antiretroviral treatment, two people become newly infected with HIV. Every day 7000 people are newly infected, including 1000 children. Weak national infrastructures, financing shortfalls and discrimination against vulnerable populations are among the factors that continue to impede access to HIV prevention, treatment, care and support services.

The Secretary-General's report, based on data submitted by 182 countries, provides five key recommendations that will be reviewed by global leaders at a UN General Assembly High Level Meeting on AIDS, June 8-10, 2011.

"World leaders have a unique opportunity at this critical moment to evaluate achievements and gaps in the global AIDS response," said Secretary-General Ban Ki-moon at the press briefing in the Kenyan capital. "We must take bold decisions that will dramatically transform the AIDS response and help us move towards an HIV-free generation."

"Thirty years into the epidemic, it is imperative for us to re-energize the response today for success in the years ahead," said UNAIDS Executive Director Michel Sidibé, who joined Mr. Ban for the launch of the report. "Gains in HIV prevention and antiretroviral treatment are significant, but we need to do more to stop people from becoming infected -- an HIV prevention revolution is needed now more than ever."

Rebecca Auma Awiti, a mother living with HIV and field coordinator with the non-governmental organization Women Fighting AIDS in Kenya told her story at the press conference. "Thanks to the universal access movement, my three children were born HIV-free and I am able to see them grow up because of treatment access," she said.

Mobilizing for impact

In the report there are five recommendations made by the UN Secretary-General to strengthen the AIDS response:
Harness the energy of young people for an HIV prevention revolution;
Revitalize the push towards achieving universal access to HIV prevention, treatment, care and support by 2015;
Work with countries to make HIV programs more cost effective, efficient and sustainable;
Promote the health, human rights and dignity of women and girls;
Ensure mutual accountability in the AIDS response to translate commitments into action.

The Secretary-General calls upon all stakeholders to support the recommendations in the report and use them to work towards realizing six global targets:

- Reduce by 50% the sexual transmission of HIV -- including among key populations, such as young people, men who have sex with men, in the context of sex work; and prevent all new HIV infections as a result of injecting drug use;
- Eliminate HIV transmission from mother to child;
- Reduce by 50% tuberculosis deaths in people living with HIV;
- Ensure HIV treatment for 13 million people;
- Reduce by 50% the number of countries with HIV-related restrictions on entry, stay and residence;
- Ensure equal access to education for children orphaned and made vulnerable by AIDS.

As international funding for HIV assistance declined for the first time in 2009, the report encourages countries to prioritize funding for HIV programs, including low- and middle-income countries that have the ability to cover their own HIV-related costs. It also stresses the importance of shared responsibility and accountability to ensure the AIDS response has sufficient resources for the coming years.

The report and more information about the High Level Meeting on AIDS can be found online at: http://unaids.org/en/aboutunaids/unitednationsdeclarationsandgoals/2011highlevelmeetingonaids.

Sources

Monkeys provide malaria reservoir for human disease in Southeast Asia

Monkeys infected with an emerging malaria strain are providing a reservoir for human disease in Southeast Asia, according to research published today. The Wellcome Trust funded study confirms that the species has not yet adapted to humans and that monkeys are the main source of infection.

Malaria is a potentially deadly disease that kills over a million people each year. The disease is caused by malaria parasites, which are transmitted by infected mosquitoes and injected into the bloodstream.

There are five species of malaria parasite that are known to cause disease in humans, of which Plasmodium knowlesi is the most recently identified. Previously thought to only infect monkeys, researchers have shown that human P. knowlesi infections are widely distributed in Southeast Asia and that it is a significant cause of malaria in Malaysian Borneo. Until now, it was not clear whether the infection is transmitted from person to person, or is passed over from infected monkeys.

Researchers led by Professor Balbir Singh at the Malaria Research Centre, Universiti Malaysia Sarawak, collaborating with Sarawak State Health Department, St George's University of London and the London School of Hygiene and Tropical Medicine, examined blood samples from 108 wild macaques from different locations around the Sarawak division in Malaysian Borneo. Their results reveal that 78% were infected with the P. knowlesi species of malaria parasite, and many were infected with one or more of four other species of monkey malaria parasites that have not yet been found in humans.

By comparing the molecular identity of the parasites from monkeys and those isolated from patients with knowlesi malaria, the team were able to build a picture of the evolutionary history of the parasite and its preferred host. Their analysis reveals that transmission of the knowlesi species is more common amongst wild monkeys, than from monkeys to humans, and that monkeys remain the dominant host.

"Our findings strongly indicate that P. knowlesi is a zoonosis in this area, that is to say it is passed by mosquitoes from infected monkeys to humans, with monkeys acting as a reservoir host," explains Professor Singh. "However, with deforestation threatening the monkeys' habitat and increases in the
human population, it's easy to see how this species of malaria could switch to humans as the preferred host. This would also hamper current efforts aimed at eliminating malaria."

Based on the molecular data, the researchers estimate that the knowlesi malaria species evolved from its ancestral species between 98,000 and 478,000 years ago. This predates human settlement in the area, meaning that monkeys are mostly likely to have been the initial host for the parasite when the species first emerged. This estimate also indicates that the species is as old as, or older than, the two most common human malaria parasites, *P. falciparum* and *P. vivax*.

The study is published today in the journal *PLoS Pathogens*. (A/7/2011)

**Common Dietary Fat and Intestinal Microbes Linked to Heart Disease**

ScienceDaily (Apr. 6, 2011) — A new pathway has been discovered that links a common dietary lipid and intestinal microflora with an increased risk of heart disease, according to a Cleveland Clinic study published in the latest issue of *Nature*.

The study shows that people who eat a diet containing a common nutrient found in animal products (such as eggs, liver and other meats, cheese and other dairy products, fish, shellfish) are not predisposed to cardiovascular disease solely on their genetic make-up, but rather, how the micro-organisms that live in our digestive tracts metabolize a specific lipid -- phosphatidyl choline (also called lecithin). Lecithin and its metabolite, choline, are also found in many commercial baked goods, dietary supplements, and even children's vitamins.

The study examined clinical data from 1,875 patients who were referred for cardiac evaluation, as well as plasma samples from mice. When fed to mice, lecithin and choline were converted to a heart disease-forming product by the intestinal microbes, which promoted fatty plaque deposits to form within arteries (atherosclerosis); in humans, higher blood levels of choline and the heart disease forming microorganism products are strongly associated with increased cardiovascular disease risk.

"When two people both eat a similar diet but one gets heart disease and the other doesn’t, we currently think the cardiac disease develops because of their genetic differences; but our studies show that is only a part of the equation," said Stanley Hazen, M.D., Ph.D., Staff in Lerner Research Institute’s Department of Cell Biology and the Heart and Vascular Institute's Department of Cardiovascular Medicine and Section Head of Preventive Cardiology & Rehabilitation at Cleveland Clinic, and senior author of the study. "Actually, differences in gut flora metabolism of the diet from one person to another appear to have a big effect on whether one develops heart disease. Gut flora is a filter for our largest environmental exposure -- what we eat."

Dr. Hazen added, "Another remarkable finding is that choline -- a natural semi-essential vitamin -- when taken in excess, promoted atherosclerotic heart disease. Over the past few years we have seen a huge increase in the addition of choline into multi-vitamins -- even in those marketed to our children -- yet it is this same substance that our study shows the gut flora can convert into something that has a direct, negative impact on heart disease risk by forming an atherosclerosis-causing by-product."

In studies of more than 2,000 subjects altogether, blood levels of three metabolites of the dietary lipid lecithin were shown to strongly predict risk for cardiovascular disease: choline (a B-complex vitamin), trimethylamine N-oxide (TMAO, a product that requires gut flora to be produced and is derived from the choline group of the lipid) and betaine (a metabolite of choline).

"The studies identify TMAO as a blood test that can be used in subjects to see who is especially at risk for cardiac disease, and in need of more strict dietary intervention to lower their cardiac risk," Dr. Hazen said.

Healthy amounts of choline, betaine and TMAO are found in many fruits, vegetables and fish. These three metabolites are commonly marketed as direct-to-consumer supplements, supposedly offering increased brain health, weight loss and/or muscle growth.

These compounds also are commonly used as feed additives for cattle, poultry or fish because they may make muscle grow faster; whether muscle from such livestock have higher levels of these compounds remains unknown.

"Knowing that gut flora generates a pro-atherosclerotic metabolite from a common dietary lipid opens up new opportunities for improved diagnostics, prevention and treatment of heart disease," Dr. Hazen said. "These studies suggest we can intelligently design a heart healthy yogurt or other form of probiotic for preventing heart disease in the future. It also appears there is a need for considering the risk vs. benefits of some commonly used supplements."

**Journal Reference:**
HIV Partner Notification Is Effective and Feasible in Sub-Saharan Africa: Opportunities for HIV Treatment and Prevention

Journal of Acquired Immune Deficiency Syndromes Vol. 56; No. 5: P. 437-442, (04..2011) Lillian B. Brown, PhD; and others

Many African countries lack standardized HIV partner notification procedures, and the efficacy of PN has not been evaluated in developing countries, the authors of the current study noted. Brown and colleagues conducted a prospective trial of HIV PN in Malawi among newly diagnosed patients presenting to two hospital-based outpatient STD clinics in Lilongwe.

Index patients were randomized to one of three PN methods: passive or “self-referral,” where index patients notify their own partners; contract referral, where the patient is given 10 days to notify partners, after which a health care provider contacts partners who have not presented for counseling and testing; and provider referral, wherein the provider notifies partners directly.

The 245 index patients identified 302 sex partners and locating information for 252, among whom 107 returned for HIV testing and counseling. For passive referral, 20 of 82 partners presented to the clinics (24 percent; 95 percent confidence interval: 15 percent to 34 percent), compared with 45 of 88 (51 percent; 95 CI: 41 percent to 62 percent) for contract PN and 42 of 82 (51 percent; 95 percent CI: 40 percent to 62 percent) in the provider referral arm (P<0.001).

Among the 107 returning partners, 67 were HIV-infected (64 percent), including 54 newly diagnosed (81 percent).

“This study provides the first evidence of the effectiveness of partner notification in sub-Saharan Africa,” Brown and colleagues wrote. “Active partner notification was feasible, acceptable and effective among sexually transmitted infections clinic patients. Partner notification will increase early referral to care and facilitate risk reduction among high-risk uninfected partners.”

This trial enrolled 90 percent of eligible patients, and most index cases were women, married and only named a single sex partner, independent consultant John J. Potterat observed in an accompanying editorial, “Puzzling Observations in a Trial of HIV Partner Notifications in Sub-Saharan Africa” (2011;56(5):381-383). Of 302 partners identified (1.25 per index), nearly three-quarters were main partners, he wrote. Index patients reported they intended to continue sexual relations with nearly three-quarters of partners identified. Almost all successful referrals were main partners, and 45 percent of all those tested were serodiscordant, Potterat wrote.

Peripheral Neuropathy Still Common, Capsaicin Patch Can Help

**SUMMARY:** Nerve damage in the feet remains common among people with HIV in the ART era, though is often asymptomatic. A patch containing capsaicin -- derived from hot peppers -- relieved pain in people with HIV-associated neuropathy, researchers reported at a recent pain conference.
Peripheral neuropathy (PN) is nerve damage that can be painful and debilitating, typically affecting the feet and lower legs. Neuropathy is a known side effect of some antiretroviral drugs, particularly the older "D-drugs," didanosine (ddI; Videx) and stavudine (d4T; Zerit); HIV infection itself may also play a role. Incidence of PN has not been studied as extensively since the advent of more tolerable antiretroviral therapy (ART).

As described in the March 10, 2011, advance online edition of AIDS, Scott Evans from Harvard School of Public Health and colleagues estimated how often signs and symptoms of neuropathy occurred after initiation of combination ART among treatment-naive HIV patients. They evaluated risk factors for PN overall and for symptomatic PN, recovery from PN after discontinuation of neurotoxic ART, and absence of PN while on neurotoxic ART regimens.

This analysis included participants in the ACTG Longitudinal Linked Randomized Trials (ALLRT) cohort -- made up of participants enrolled in a number of prospective ACTG clinical trials of ART -- who initiated ART in randomized trials for treatment-naive patients.

A total of 2141 people were followed from January 2000 through June 2007; a majority of participants were men. Overall they had well-controlled HIV disease after starting therapy; more that 80% had low viral load (< 400 copies/mL) and 70% had a CD4 T-cell count above 350 cells/mm3.

Participants were screened annually for signs and symptoms of PN, defined as at least mild loss of vibration sensation in both great toes, or absent or hypoactive (reduced) ankle reflexes in both legs. Symptomatic PN was defined as bilateral (both sides) symptoms.

**Results**

- At baseline nearly 25% of participants had PN detected by testing, and 4% reported neuropathy symptoms.
- The overall rate of PN at 3 years was 32%.
- The rate of symptomatic PN was much lower, at 9%.
- Among participants who used neurotoxic antiretroviral drugs, 27% had PN detectable by testing and 9% experienced PN symptoms.
- Among affected patients, 54% continued to have detectable PN and 18% continued to have symptom after stopping neurotoxic drugs.
- In a multivariate analysis, risk factors associated with a higher likelihood of PN included older age and current use of neurotoxic antiretroviral drugs.
- Factors associated with higher risk of symptomatic PN included older age, neurotoxic ART use, and history of diabetes.
- Older patients and those currently taking protease inhibitors were more likely to experience PN while on neurotoxic ART.
- Older people and protease inhibitor recipients were also more likely to have symptomatic neuropathy while on neurotoxic ART, as were taller individuals and those with a history of diabetes.
- Older individuals were less likely to recover after discontinuation of neurotoxic ART.

Based on these findings, the investigators concluded, "Signs of PN remain despite virologic/immunologic control but frequently occurs without symptoms."

"Peripheral neuropathy in HIV patients persists despite improved immunological function and virologic control associated with combination antiretroviral therapy and decreased use of neuro-toxic [antiretroviral drugs]," they elaborated in their discussion.

PN is a concern as a growing proportion of people with HIV reach older age. Notably, however, only about one-quarter of patients in this study who had PN detectable with special testing were actually bothered by neuropathy symptoms. This suggests that a considerable proportion of people who once used
neuro-toxic drugs may have switched to more tolerable treatment before extensive nerve damage resulted in clinical manifestations.

**Capsaicin Patch**

PN can be difficult to manage, but new therapies are under study. MedPage Today recently reported findings from a study of a patch containing capsaicin -- a component that gives chili peppers their heat -- presented at this month's American Academy of Pain Medicine (AAPM) annual meeting.

Stephen Brown from the AIDS Research Alliance in Los Angeles presented data from 2 randomized, controlled studies that together included 338 participants with HIV-associated neuropathic pain.

Patients who applied an 8% capsaicin patch for a single 30-minute period reported an average 27% decrease in their Numeric Pain Rating Scale score, compared with a mean 16% decrease for those using a 0.04% capsaicin control patch. More than one-third of those using the stronger patch reported at least a 2-point pain score reduction. The most common side effects were transient pain and redness at the application site (participants received lidocaine prior to application since the patch can be painful).

NeurogesX, the company that sponsored the study, is seeking approval of the patch for HIV-related neuropathy; it is currently approved (under the brand name Qutenza) for post-herpetic neuralgia, or shingles.

**Uncommon Resistance Mutations Can Cause First-Line Treatment Failure**

SUMMARY: Low-frequency drug-resistance mutations, especially those related to NNRTIs, can lead to virological failure among HIV patients starting antiretroviral therapy (ART) for the first time.

By Liz Highleyman

It is well known that highly treatment-experienced people may not achieve sustained HIV suppression due to drug resistance, which in many cases emerged due to sequential monotherapy or dual therapy in the pre-ART era. Less than optimal adherence can also contribute to development of resistance. But the effects of pre-existing low-frequency or minority resistance mutations are not as well understand.

As described in the April 6, 2011, Journal of the American Medical Association, Jonathan Li and Daniel Kuritzkes from Harvard Medical School and colleagues performed a systematic review to assess...
the association between pre-existing drug-resistant HIV minority variants and risk of virological failure while on first-line non-nucleoside reverse transcriptase inhibitor (NNRTI) antiretroviral regimens.

Using traditional polymerase chain reaction (PCR) amplification and population sequencing techniques, the prevalence of transmitted drug-resistance mutations in North America and Europe is estimated to be between 8% and 16%, the researchers noted as background. Standard tests detect mutations present in about 15% to 25% of an individual’s viral strains or quasi-species. But these tests may not detect the presence of less common minority resistance mutations.

The investigators reviewed published and unpublished studies of ART-naive participants initiating NNRTI-based regimens. They searched PubMed (1966 through 2010), EMBASE (1974 through 2010), conference abstracts, and article references. Authors of all studies were contacted to obtain detailed laboratory, ART, and adherence data.

Out of a total of 1263 study participants, the researchers include those with all drugs in their ART regimen fully active according to standard HIV drug-resistance testing. This left individual data from 10 studies and 985 participants available for analysis, including 808 patients in 6 cohort studies. Most (about 80%) were men and the average age was 38 years.

The investigators correlated presence of mutations with treatment failure defined as HIV RNA ≥200 copies/mL on 2 consecutive measurements 16 weeks or more after starting therapy.

**Results**

- Low-frequency drug-resistance mutations were detected in 187 of 985 participants (19%) overall, including 117 of 808 patients (14%) in cohort studies.
- All had minority reverse transcriptase gene mutations, including K103N and Y181C (which confer resistance to NNRTIs) and M184V and K65R (which confer resistance to nucleoside/nucleoside reverse transcriptase inhibitors [NRTIs]).
- In a pooled analysis, low-frequency resistance mutations were associated with a significantly increased risk of virological failure after controlling for adherence, race/ethnicity, baseline CD4 cell count, and plasma viral load (hazard ratio 2.3, or more than twice the risk; P < 0.001).
- Increased risk of virological failure was most strongly associated with minority variants resistant to NNRTIs (hazard ratio 2.6; P < 0.001).
- The increased risk associated with NRTI-resistance minority variants did not reach statistical significance (hazard ratio 1.6).
- Among cohort participants with NNRTI-resistant minority variants, the overall failure rate was 37%, compared with 15% for those without rare variants (hazard ratio 3.8; P < 0.001).
- Among people in the cohort studies, 35% of participants with detectable minority resistance mutations experienced virological failure, compared with 15% of those without minority variants.
- Presence of minority resistance variants increased the risk of virological failure by 2.5 to 3.0 times, both at ≥95% and < 95% adherence.
- Presence of minority variants at a proportion of ≥1% conferred a significantly higher risk of virological failure compared with variants present at < 1%.
- Study participants with a higher proportion or quantity of drug-resistant variants had a "dose-dependent" increase in the risk of virological failure.
- In addition to drug-resistance mutations, other independent predictors of virological failure were medication adherence (hazard ratio 0.86 per 5% better adherence) and race/ethnicity.
- White participants had a lower risk of virological failure compared with blacks, Hispanics/Latinos, and people of other races/ethnicities.

Based on these findings, the study authors concluded, "In a pooled analysis, low-frequency HIV-1 drug-resistance mutations, particularly involving NNRTI resistance, were significantly associated with a dose-dependent increased risk of virologic failure with first-line ART."
"While we found a dose-dependent effect of drug-resistant minority variants on risk of virologic failure, an increased risk was detected even at very low minority variant frequencies (< 0.5% and 10-99 copies/mL)," they elaborated in their discussion.

They noted, however, that not all of the included studies tested for the most common NRTI and NNRTI mutations (though all did check for K103N), so the prevalence of minority resistant variations might actually be higher.

"The relationship between race/ethnicity and virologic failure may be mediated by factors such as socioeconomic status, drug and alcohol use, or other factors not accounted for here that may correlate with adherence and could contribute to residual confounding," the authors suggested.

More sensitive tests for drug resistance mutations (e.g., deep sequencing) are available, but are not yet widely used. The researchers calculated that approximately 11 patients would have to be screened with the most sensitive NNRTI resistance test prior to ART initiation in order to avoid 1 case of virological failure.

"These data provide a rationale for developing standardized clinical assays for the detection of NNRTI-resistant minority variants," they recommended. "Because NNRTI-based regimens are the most commonly prescribed first-line antiretroviral therapy, the clinical use of ultrasensitive screening for drug-resistant HIV could help identify individuals at greatest risk of virologic failure and allow ART to be tailored appropriately."

4/8/11

Reference

Cotrimoxazole prophylaxis for HIV-positive infants aids growth, reduces anaemia
Carole Leach-Lemens
Published: 11 April 2011
Use of daily cotrimoxazole in untreated HIV-infected infants significantly improved growth and reduced anaemia, Andrew Prendergast and colleagues reported in new findings from an observational analysis of the children enrolled in the Children with Antibiotic Prophylaxis (CHAP) trial published in the April 1 edition of Clinical Infectious Diseases.

The CHAP trial was double-blinded, randomised and placebo-controlled. It took place in Zambia from 2001 until 2003.

The study showed that cotrimoxazole, a cheap, widely available antibiotic, taken daily, reduced death and disease in HIV-infected children across all age groups and CD4 cell counts.

Cotrimoxazole is effective against malaria as well as infections that cause diarrhoea and pneumonia. While the benefits of cotrimoxazole in HIV-infected adults and children are acknowledged how it works precisely is not well understood. Its chief benefit probably lies in the prevention of bacterial lung infections.

HIV-infected children in sub-Saharan Africa are often underweight and stunted. Malnutrition and anaemia are both independently linked to death in this population.

Weight gain is a crucial component of HIV programmes for infants and children.

So the authors chose to look at whether cotrimoxazole had a specific effect on growth and anaemia in HIV-infected children.

541 HIV-infected children from one to 14 years of age were enrolled at the University Teaching Hospital in Lusaka. 268 children were randomised to get daily cotrimoxazole (240 mg for children under five years of age; 480 mg for children over five years of age) and 273 to get placebo.

Children were followed every month for the first four months, then every two months afterwards. The trial was stopped early because of the sustained and significant benefits seen in those taking cotrimoxazole.

28% of those taking cotrimoxazole died compared to 42% in the placebo group (p=0.001).

The mean CD4 cell percentage at baseline was 12.3%. The mean annual change in CD4 cell percentage was +0.14 (95% CI: -.55 to .83) for those taking cotrimoxazole and -0.37% (95% CI: -1.18 to .44) for those on placebo.

Weight and height measurements were available for all 541 children. There was a high baseline prevalence of stunting and underweight. The mean weight-for-age (WAZ) and height-for-age (HAZ) was -2.84 (SD, 1.63) and -3.25 (SD, 1.48), respectively.
Among untreated HIV-infected children taking cotrimoxazole the weight-for-age decrease was twofold lower and the height-for-age decrease threefold lower compared to children taking placebo. The difference was statistically significant; the annual change in WAZ (mean -0.15 [95% CI: -.28 to -.03 compared to -0.35 (95% CI: -.49 to -.21), heterogeneity, p=.04); and HAZ (men, -0.07 [95% CI: -.15 to -.01] compared to -0.22[95% CI: -.30 to -.13] heterogeneity, p=.01).

At the time antiretroviral treatment was not publicly available for children in Zambia. So growth among the children in the trial got worse as their HIV disease progressed. The authors suggest that future studies look at whether ART and cotrimoxazole have an additive effect on growth.

Poor growth is the result of many factors and includes an increased rate of infections, poor appetite and difficulty digesting as well as persistent diarrhoea. The authors believe that cotrimoxazole affects growth by reducing infections and diarrhoea. They note that cotrimoxazole may lower immune activation in HIV-infected children by lowering intestinal bacteria. The process of microbial translocation, whereby bacteria from the gut get into the blood system, is the primary driver of Immune-activation.

The authors note that microbial translocation is believed to cause malnutrition and stunting in HIV-infected and uninfected children alike. They add that if future studies confirm that cotrimoxazole affects microbial translocation and/or immune activation then it can be used to improve growth in HIV-uninfected children too.

Most of the children had baseline anaemia. However, those taking cotrimoxazole had a four-fold increase in levels of haemoglobin compared to those on placebo. The authors note that anaemia in HIV-infection is due to many factors, the most important of which is a failure to produce red blood cells (erythropoiesis).

It is feasible that cotrimoxazole reduces the levels of cytokines which interfere with the process of erythropoiesis, the authors add.

Policies for cotrimoxazole prophylaxis exist in most countries yet in 2007 only 4% of eligible children got it, the authors note.

The authors conclude “the current study argues for earlier identification of HIV-infected children and more widespread cotrimoxazole use, to reduce morbidity and mortality and to improve growth and anaemia where ART is unavailable. “

Where ART is available its use should be encouraged or continued; it may have an additive effect on nutrition and anaemia as well as reducing mortality as recent findings in adults have shown, they add.

Reference

Young adults who were infected at birth: the complexities of lifelong HIV are increasingly apparent
Roger Pebody
Published: 11 April 2011

Although 85% of young adults who take antiretroviral therapy have an undetectable viral load, the complexities and complications of lifelong HIV infection are becoming increasingly apparent, researchers told the British HIV Association conference in Bournemouth last week. Rates of hospital admissions, co-morbidities and lipodystrophy are high.

The psychological burden of living with HIV is also heavy. Problems with adherence, mood, anxiety, disclosure and relationships are common, with a few young people self-harming or requiring psychiatric medication.

The issues were raised in a series of studies from St. Mary’s Hospital, the London hospital which for many years has had the largest paediatric HIV clinic in the country and has more recently developed the 900 Clinic, a transitional services to help young people manage the shift from child-friendly services into an adult clinic. In addition, a national survey shed light on adherence issues for young people with HIV.

Tania Wan presented data on the health outcomes of 58 perinatally infected young people who were seen between 2006 and 2011 at the 900 Clinic. The young people transferred from paediatric clinic between the ages of 16 and 18 and their current median age is 20, with the youngest 16 and the oldest 26. Three quarters are black African; there are more women than men.

At their last follow-up, two-thirds of the young people were taking antiretroviral treatment, and 95% of this sub-group had an undetectable viral load.
However there were a considerable number of complications. A fifth of patients had a CD4 cell count below 200 cells/mm³. A few of those with undetectable viral load had failed to fully restore their immune function.

At the time of last follow-up, a quarter had chosen to discontinue antiretroviral treatment, despite considerable support and intervention from clinic staff. Just under half of this group had a CD4 cell count below 200 cells/mm³.

There have been seven pregnancies (with no HIV transmissions).

A quarter had at some stage been admitted to hospital as an inpatient, staying a median of nine days. Four had intentionally taken drug overdoses; two hospitalisations were linked to the opportunistic infections PCP and MAI; one 22 year old was admitted following a stroke and osteocronosis (loss of blood supply to the bones).

Two individuals died, at the ages of 20 and 21. One had refused antiretroviral therapy; the other had developed multiple drug resistance.

One in eight had severe lipodystrophy, with several requiring surgery or injectable fillers.

The high levels of psychological need in this group were described in a poster from Graham Frize and colleagues at St. Mary’s. For this analysis, the psychology case notes were checked for 63 young adults attending the clinic between 2008 and 2010.

Just over half were identified as having clinically significant psychological issues, whereas in this age group of the general population, the figure is 13 – 16%. These individuals were all referred for psychological interventions but a quarter did not take up the service. Young men were more likely to decline psychological services than women.

The most common problems were mood, anxiety, adherence, disclosure and relationships, but people usually presented with more than one issue.

Commonly reported stressors include difficult family relationships, lack of social support, housing problems, financial problems and health problems. Several had concerns about body image.

A quarter of clinic patients (17 people) were considered to have complex needs. Five had self-harmed by taking a drug overdose (including the four requiring hospitalisation as previously mentioned). Eight have been prescribed psychiatric medication. Four were referred for neuropsychological testing due to concerns about the impact of neurocognitive impairment on their functioning.

Given the results of this analysis, St. Mary’s have decided to offer an annual psychological review for this group of patients. This will involve tests to assess psychological distress as well as physical and mental health-related quality of life.

Adherence to medication is challenging for this group and a problem which drives many of the health complications described above. Another poster from St. Mary’s reviewed adherence and treatment response in young people, both while they were attending the paediatric clinic and later when they attended adult services.

Individuals who had good self-reported adherence in childhood generally maintained the same behaviour as young adults and continued to have good treatment response. Similarly, those with poor adherence in childhood most commonly continued to have difficulties, with sub-optimal clinical outcomes.

This is despite the provision of intensive support in both the paediatric and adult services including provision from psychologists, peers and the voluntary sector; practical adherence aids; directly observed therapy and the use of gastrostomy tubes into the stomach.

The researchers suggest that as adherence patterns appear to be established in childhood, it is essential to support adherence when children begin therapy in order to promote long-term adherence and survival.

The final study, from Susan McDonald and colleagues is a national survey of young people with HIV aged 12 to 24, in order to review their feelings and concerns about adherence. A total of 138 took part, with a median age of 16, and once again there was greater participation from females than males.

Just under two-thirds (62%) reported adhering to at least 95% of their doses, mirroring the 66% who said that their viral load was undetectable.

Only a third used practical adherence tools such as pill boxes, alarms, keeping medication in a place that helps them remember or carrying a spare dose with them.

When asked what helped them adhere, the participants were more likely to mention reminders and support from family, carers and peers - just under half mentioned this. Not being able to take treatment in front of family or friends (due to disclosure issues) negatively affected the adherence on a fifth of
respondents. Some mentioned that if they didn’t need to keep HIV such a secret, their adherence would improve.

Drug side effects were described as a factor that had contributed to treatment interruptions and to missing doses by many participants. Fewer side effects, fewer pills and once-daily regimens were thought to help adherence.

One respondent described the reasons behind a treatment interruption: “Feeling depressed and there are times when you don’t feel like taking them because you feel well and when you feel them you feel ill.” Another respondent’s comment on what could help adherence was: “I don’t know really, I like the challenge, every day’s a victory, peer support has given me insight.”

References
2. Frize G et al. Psychology service evaluation in a clinic for young people (over 16 years) living with HIV and transitioning to adult care. 17th annual British HIV Association conference, Bournemouth, abstract P168, 2011.

Brain impairment in people with HIV may not be as common as we thought
Gus Cairns
Published: 11 April 2011

Two studies presented at the 17th British HIV Association (BHIVA) conference last week suggest that the proportion of people who have subtle brain impairment due to HIV may not be as high as previously thought, and may in fact be little higher than in the general population.

Several studies measuring neurocognitive impairment (deficits in memory, thinking and movement) in people with HIV in the last few years have concluded that a high proportion of people with HIV have subtle impairments. These may not cause symptoms that interfere with daily life, but can be detected by psychological tests.

About 16% of the general population has some degree of neurocognitive deficit. It therefore caused a lot of concern when in 2010 the large CHARTER trial in the USA found that 52% of 1526 people with HIV had evidence of neurocognitive impairment.

A quarter of these people had other conditions that were probably the major cause of their brain impairment, but that still meant that 39% of all HIV-positive patients had brain impairment without any other obvious cause, and 36% of patients who had never had an HIV-related illness. Of these 71%, or 28% of the entire group, had no obvious neurological symptoms. CHARTER, therefore, suggested that HIV more than doubled the risk of brain impairment in otherwise healthy people, raising concerns that it might become even more common with age.

One study presented at BHIVA, however, found a rate of asymptomatic neurocognitive impairment of only 19% in a group of patients with suppressed viral loads, very little in excess of the general population rate. Another study found that young people who had been born with HIV had rates of neurocognitive impairment no higher than their HIV-negative siblings. This study, and a third study that looked at rates of neurocognitive impairment in the over-50s, found some evidence that some psychological tests that rely on self-report might not be detecting actual difficulties in thinking and memory, but rather people’s fear of them.

The St Mary’s Study
Dr Lucy Garvey from St Mary’s and Hammersmith Hospitals in west London reported on a survey (which won a prize for best presentation at the conference) of 101 patients who were on stable antiretroviral therapy without any obvious neurological symptoms or other illnesses. They had all had HIV for more than six months.

The study subjects were given two types of psychological test, a 20-minute computerised cognitive assessment test called Cogstate, and the International HIV Dementia Scale (IHDS), a short, validated screening test for dementia employing three simple memory and motor tasks.

Neurocognitive impairment was defined as scores more than one standard deviation below the mean age-matched population data in at least two areas of functioning - roughly within the lowest one-sixth of performance scores.
The median age of the subjects was 53, and the majority (77%) were white men. They had been HIV-positive for an average of 14 years, with a mean CD4 count of 559 and lowest-ever CD4 count (nadir) of 185. A high proportion – 25% - had hepatitis C, which is also associated with neurocognitive disorders.

The overall rate of neurocognitive impairment was 19% in this group, only 3% above the rate in the general population. The pattern of domains affected was familiar from other studies of people with HIV, in that fine muscular movement, multitasking and executive function (prioritising and planning) were particularly impaired, and CD4 nadir was associated with a high IHDS score, but nonetheless the impairments seen were slight.

“Many cohorts have reported HIV-associated neurological disorder, but their antiretroviral therapy status and health have been widely variable,” commented Dr Garvey. “This is one of the first studies to look at neurocognitive impairment only in stable HIV-asymptomatic patients on suppressive antiretroviral therapy.”

The St Mary’s team will now conduct further studies to look at neurocognitive disorder in drug-naive patients with unsuppressed HIV.

Young people and brain impairment

The results from this study were echoed by another study from St Mary’s that looked at neurocognitive function in young people who had been born with HIV. It studied 31 young people aged 16-25 (mean age 20) and compared their performance with 14 of their HIV-negative siblings. The two groups were matched for age, ethnicity (both 85% black African) and gender (33% and 29% respectively were male in the positive and negative groups). Seventy-nine per cent of the positive subjects were on antiretrovirals of whom 70% were virally suppressed (55% of the whole group).

These subjects were given the Cogstate computerised tests and the IHDS, and were also given the prospective and retrospective memory scale (PRMQ) questionnaire, a self-reported rating of problems with recall and retention of information. A minority of both groups were also given an MRI brain scan to detect signs of inflammation.

The positive and negative group had identical scores on the IHDS and on the Cogstate test in all domains. The PRMQ score was significantly worse (p=0.023) for the HIV-positive young people, and there were also high levels of activity of certain neurotransmitters in the basal ganglia area of the brain, a finding seen in other studies.

However presenter Jane Ashby commented that the PRMQ questionnaire, as a self-report, could measure subjects' concern about memory problems as much as actual ones, and so far no study in HIV has actually established whether the inflammation seen in MRI scans is actually associated with neurocognitive performance.

Screening for brain impairment

The idea that some psychological tools might be reporting HIV-positive people’s fears of dementia rather than actual impairment, and might over-report neurological problems, has led London’s first dedicated HIV clinic for people over 50 at the Chelsea and Westminster Hospital to include two ten-minute psychological questionnaires for generalised anxiety disorder and depression as standard first steps in psychological assessment of patients, only proceeding to tests for neurological function once these are eliminated.

The researchers comment that “high levels of anxiety, depression and concern about cognitive function” are common in older patients and that “memory loss, mental slowing and psychomotor disorder are common manifestations of these conditions” and should therefore be assessed and treated first.

References

Planned Parenthood, Abortion and the Budget Fight

Associated Press, (04.09.2011) Donna Cassata

Central to the recent congressional showdown over the federal budget was the 90-year-old Planned Parenthood Federation of America. Republicans wanted any legislation keeping the government running to withhold funding from the health care - and abortion - provider, calling for that money to go to the states instead. Democrats refused, saying laws already prohibit the organization from using tax dollars to
provide abortions, and arguing that the funding provides poor women with basic reproductive health services.

Late Friday evening, the White House and congressional negotiators reached a deal on the budget and a compromise on Planned Parenthood funding: The Senate will vote on the money, and likely will reject the House push to cut off funding.

According to Planned Parenthood, abortions comprise just 3 percent of its total health care services. Last year, the group performed roughly 330,000 abortions. Its staff also provided STD testing and treatment for some 4 million individuals, and conducted 1 million cervical cancer and 830,000 breast screenings.

The organization said it receives $363 million in federal funds, primarily from the Title X and Medicaid programs. Planned Parenthood’s annual operating budget is $1.1 billion. The group is barred from using taxpayer funds for abortion—except in cases of rape, incest, or when a mother’s life is at risk—under the 1976 Hyde Amendment, which is attached annually to the congressional budget.

While the matter is settled for now, the fight over federal funding of Planned Parenthood will resume. After Congress agrees on a budget for the current fiscal year, it must set spending limits for the next budget.

**STD/HIV Risk Among Adults in the Primary Care Setting: Are We Adequately Addressing Our Patients’ Needs?**

Sexually Transmitted Diseases Vol. 38; No. 1: P. 30-32, (01.01.2011) Diana Nurutdinova; Shilpa Rao; Enbal Shacham; Hillary Reno; Edgar Turner Overton

The authors noted that risk behavior surveys often target STD clinic patients, but less research addresses risk behaviors in primary care settings. The current cross-sectional study was performed at a university adult primary care clinic and evaluated risk behaviors using an anonymous, self-administered survey. The data collected included demographics, sexual history, condom use and confidence discussing STDs.

The respondents were predominately female (69 percent) and black (67 percent); in all, 718 surveys were completed. Forty-four percent said they had never been asked about their sexual health by a primary care provider, and 18 percent said they had never had a gender-specific genital examination.

Among the 394 persons reporting sexual activity in the previous three months, 58 percent said they never used a condom, and 33 percent stated their intention not to use a condom during their next sexual encounter. Approximately one-third had never been tested for HIV and did not know their partner’s HIV status. A history of STD was reported by one-third, while 32 percent said they felt uncomfortable talking about STDs with their primary care provider.

“Our data demonstrate that sexual health is infrequently addressed despite high rates of previous STDs and low condom use in this population,” the authors concluded. “Identifying barriers to determining sexual risk behaviors in the primary care setting will help to expand testing strategies for HIV and other STDs.”

**Cancer burden shifts for people with HIV/AIDS**

The number of cancers and the types of cancers among people living with AIDS in the U.S. have changed dramatically during the 15-year period from 1991-2005, according to an article published online April 11th in the Journal of the National Cancer Institute.

It is known that HIV-infected patients face an increased risk of Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer—the AIDS-defining cancers—and that the incidence of these cancers dropped when highly active anti-retroviral therapy (HAART) became available in the mid-1990s. People living with HIV and AIDS are also known to have an elevated risk of certain other cancers, including lung, anal, and liver cancer, and Hodgkin lymphoma. These are known among AIDS researchers as non-AIDS-defining cancers.

To estimate the numbers of AIDS-defining and non-AIDS-defining cancers in people with AIDS in the U.S., researchers from the National Cancer Institute (NCI) in Bethesda, Md, and the Centers for Disease Control and Prevention (CDC) in Atlanta, led by Meredith S. Shiels, Ph.D., at the NCI, used data from the U.S. HIV/AIDS Cancer Match Study and from the CDC. They evaluated data from three calendar periods: 1991-1995 (pre-HAART); 1996-2000 (early-HAART); and 2001-2005 (late-HAART).

As expected, the researchers found that the number of AIDS-defining cancers overall dropped markedly from the pre-HAART (34,587 cases) to the late-HAART period (10,325 cases). In contrast, the
non-AIDS-defining cancers increased three-fold between the early period (3,193 cases) and the late period (10,059 cases). In fact, since 2003, fewer than half of the all cancers have been AIDS-defining cancers.

Also, to estimate cancer burden in people with HIV but not AIDS, the authors used data from 34 states from 2004-2007 and found lung cancer to be the most common malignancy in the HIV-only population, comprising 20% of all cancers.

Aging and increased survival are largely responsible for the patterns observed, according to the authors. From 1991 to 2005, the AIDS population in the U.S. increased fourfold, primarily because of an increase in patients aged 40 years or older who are living longer because of HAART. Particularly as the number of older people living with AIDS has grown, the burden of cancer has shifted, resulting in a new and serious public health issue, according to the authors.

"The growing burden of non-AIDS-defining cancers highlights the need for cancer prevention and early detection among HIV-infected people," the authors write. They suggest various strategies, such as smoking cessation to help prevent lung cancer; prevention and treatment of hepatitis B and C infections to reduce the risk of liver cancer; and further evaluation of screening tests for anal cancer.

The authors note that cancer treatments must be tailored to people with HIV. "As individual centers may see few cancers in HIV-infected people, multicenter consortia are needed to comprehensively evaluate cancer treatment protocols in this population," they write.

**Stress Wrecks Intestinal Bacteria, Could Keep Immune System On Idle**

COLUMBUS, Ohio – Stress not only sends the human immune system into overdrive – it can also wreak havoc on the trillions of bacteria that work and thrive inside our digestive system.

New research suggests that this may be important because those bacteria play a significant role in triggering the innate immune system to stay slightly active, and thereby prepared to quickly spring into action in the face of an infection.

But exactly how stress makes these changes in these bacteria still isn’t quite clear, researchers say.

"Since graduate school, I’ve been interested in how stress affects the bacteria naturally in our bodies,’ explained Michael Bailey, an assistant professor of dentistry and member of the Institute for Behavioral Medicine Research at Ohio State University.

"Even though we’ve known that stress changes these bacteria, we didn’t really understand what that meant or if there was any sort of biological function associated with effects on these bacteria."

The new study appears in the current issue of the journal *Brain, Behavior and Immunity*.

The human digestive tract is a universe filled with microbes. There are probably 100 trillion bacteria in the average human, 90 percent of which live mainly in the intestine. They easily outnumber human cells 10-to-one in each person.

Bailey and colleagues turned to mice to better understand the roles that bacteria play in immune balance. They ran a series of experiments using a common stressor for these animals. For two hours daily for six days, an aggressive mouse was placed in a cage of a group of more docile mice.

At the end of the string of experiments, blood samples were taken from both stressed animals and matched mice from a control group, along with samples of material from inside each animal’s intestine. The blood samples were analyzed to detect the levels of two biomarkers used to gauge stress – a cytokine called interleukin-6 (IL-6) and a protein called MCP-1 that summons macrophages, or scavenger cells, to the site of an infection.

From the intestinal samples, Bailey’s team could determine the relative proportion of at least 30 types of bacteria residing there.

Compared to the control mice, the stressed animals showed two marked differences: The proportion of one important type of bacteria in the gut – *Bacteroides* – fell by 20 to 25 percent while another type – *Clostridium* – increased a similar amount. Also, levels of the two biomarkers, IL-6 and MCP-1, jumped 10-fold in the stressed mice, compared to controls.

The researchers then treated stressed mice with broad-spectrum antibiotics that could kill as much as 90 percent of the intestinal bacteria for a short period. When they again looked at the two immune biomarkers in the stressed mice, they saw only a doubling of IL-6 and MCP-1 – an increase only one-fifth as much.

"We know now that if we knock the population of bacteria down with antibiotics, we don’t have the same innate immune response,” Bailey said. “That showed that the bacteria are involved in the ability of stress to prime the innate immune system.”
He said that the research shows that some of the changes in systemic immunity in the body can be influenced by changes in these bacterial colonies, a result that reinforces the idea that they have a broader effect on the immune response.

The next step, the researchers say, is to better understand the roles that the bacteria play in activating the immune system, and to determine if other factors are playing a key role in the process.

**Letting There Be More Mosquitoes May Lead to Fewer Malaria Deaths, Say Researchers**

ScienceDaily (Apr. 11, 2011) — It may seem counter-intuitive at first but letting mosquitoes grow up and breed may be part of the solution to tackling the devastating impact of malaria. A team of researchers led by Dr Stephen Gourley of the University of Surrey’s Mathematics Department have used mathematical modelling to examine why conventional insecticides used against the insects that transmit the disease responsible for millions of deaths a year, can quickly become ineffective in areas of intensive use. Their answers may lead to unprecedented advances in malaria control.

Mosquitoes can become resistant to commonly used insecticides surprisingly rapidly and spraying them while young simply imposes intense selection pressure favouring resistant insects.

have suggested that a new kind of late-acting insecticide could slow this process and lead to insecticides which would remain effective over a much longer period of time. The strategy aims to exploit the fact that mosquitoes only become able to infect humans with malaria late in their lifetime, due to a relatively long latency stage. This means that the delayed action insecticide doesn’t result in increased infection rates while the younger insects remain alive.

It could, however, mean a rise in the number of troublesome, but non-malarial, mosquitoes.

Dr Gourley said: "There is a trade-off between effective prevention of malaria transmission by mosquitoes and having to live with mosquito bites involving no malarial transmission."

2008 malaria caused almost one million deaths and remains one of the leading causes of child mortality in Africa. More of the insects in general, but fewer with the deadly disease, may be a price worth paying.

Conventional insecticides, such as DDT, kill mosquitoes as soon as they are exposed to the chemical. But while this approach works well in the short term, its indiscriminate action speeds up the evolution of the insect towards insecticide resistance.

In particular, because the insecticide acts on female mosquitoes before they lay eggs, this causes intense selection pressure towards insecticide-resistant females who then pass on this resistance to their offspring.

Dr Gourley’s team used mathematical models to predict the effect of an insecticide that only acts after a time delay, once the mosquitoes have laid their eggs. Because this results in a much lessened selection pressure on resistant mosquitoes, the team discovered that resistance evolves much more slowly with this type of insecticide.

The technique could result in vastly improved malaria control in areas where resistance to current insecticides is rife amongst mosquitoes.

**Journal Reference:**


**New Technique Tracks Viral Infections, Aids Development of Antiviral Drugs**

ScienceDaily (Apr. 11, 2011) — Scientists at the Naval Research Laboratory Center for Bio-Molecular Science and Engineering have developed a method to detect the presence of viruses in cells and to study their growth. Targeting a virus that has ribonucleic acid (RNA) as its genetic makeup, the new technique referred to as locked nucleic acid (LNA) flow cytometry-fluorescence in situ hybridization (flow-FISH), involves the binding of an LNA probe to viral RNA.

While individual parts of the technique have been developed previously, Drs. Kelly Robertson and Eddie Chang, in collaboration with researchers at the NRL Lab for Biosensors and Biomaterials, demonstrate for the first time that the combination of LNA probes with flow-FISH can be used to quantify viral RNA in infected cells. This also allows the scientists to monitor the changes in viral RNA accompanying antiviral drug treatment.

Once the probe is bound to the viral RNA inside mammalian cells, it is tagged with a fluorescent dye, then thousands of these tagged cells are measured rapidly by "flow cytometry" -- a method for counting
and examining microscopic particles, such as cells and chromosomes, by suspending them in a stream of fluid and passing them by an electronic detection apparatus.

"The ability to rapidly measure thousands of cells for the presence of virus, sets this technique apart from currently used methods to monitor viral replication," said Robertson.

Traditionally, antibodies used to detect viruses must be produced and calibrated for each specific strain and are highly susceptible to viral mutations. Assays commonly used for quantifying viral loads and for drug development can be time consuming and rely on visible signs of cell damage, which is not produced in all viruses and can take long periods of time to occur.

such as quantitative reverse transcription-polymerase chain reaction (qRT-PCR), microarrays, and enzyme-linked immunosorbent assays (ELISAs), while highly sensitive, involve the lysis [the breaking down] of cells prior to measurement and are therefore unable to provide information about cellular viability, infected cell phenotypes, percentage of infected cells or the variation in infection among a cell population. The LNA probe differs from traditional nucleotide probes by binding more tightly to its target RNA.

LNA-flow FISH presents a fast and easy way to screen for compounds with antiviral activity and could be adapted for monitoring infections in the blood for vaccine therapy and development. This method adds a necessary tool for several emerging areas in cell biology that enables the use of high throughput measurements for entire populations and improves statistical analyses.

"This method can be expanded by adding more than one kind of LNA probe to enable multiple detection of different viral and host RNA," adds Robertson. "The multiplexing enhancement can be used to better understand infectious agents, allowing this technique to be used to aid in the development of antiviral drugs for a variety of viruses."

LNA flow-FISH offers an advantage over other techniques due to its simplicity and superiority. Methods involving genetic recombination of the virus to express a fluorescent protein as a means to mark the presence of virus can utilize flow cytometry for large-batch analysis of infected cells. However, an exception to this approach is viral strains that have not acquired genetic mutations, known as wild-type viruses (such as strains of Human Immunodeficiency Virus-HIV), which would require a large initial investment of labor for engineering each virus of interest.

**Big Picture of How Interferon-Induced Genes Launch Antiviral Defenses Revealed**

ScienceDaily (Apr. 10, 2011) — When viruses attack, one molecule more than any other fights back. Interferon triggers the activation of more than 350 genes, and despite the obvious connection, the vast majority have never been tested for antiviral properties. A team of researchers, led by scientists from Rockefeller University, for the first time has carried out a comprehensive, systematic evaluation of the antiviral activity of interferon-induced factors.

The findings, published online April 10 in the journal *Nature*, are a first step toward unraveling how these naturally occurring molecules work to inhibit viruses.

"We hope this study will open the door to future work on the mechanisms of antiviral molecules," says first author John Schoggins, a postdoctoral associate in Charles M. Rice's Laboratory of Virology and Infectious Disease at Rockefeller. "Such mechanistic studies may set the stage for the development of new and much needed drugs to combat a diverse array of viruses that pose significant health threats to people worldwide."

The researchers were interested in type I interferon, a cellular molecule that is made when a person becomes infected with certain viruses. Type I Interferon is used clinically in the treatment of some viral diseases, such as hepatitis C, and its presence has been shown to significantly limit the severity of certain viral infections.

Schoggins and his colleagues, including researchers from the Aaron Diamond AIDS Research Center and the Howard Hughes Medical Institute, systematically evaluated the majority of common interferon-induced genes, one by one, to determine which of them had antiviral activity against a panel of disease-causing viruses, including the hepatitis C virus, HIV, West Nile virus, the yellow fever virus and chikungunya virus.

The scientists used a cell-based "screen" to measure the ability of each gene to halt the growth of the viruses: One by one, genes were delivered into the cells that were then infected with virus. In cells that had no interferon-induced genes delivered, Schoggins and his team observed normal levels of virus replication. In cells that had interferon-induced genes delivered, they occasionally found "hits" that could significantly impair virus replication.
Overall, Schoggins and his colleagues found that each virus tested was susceptible to inhibition by a unique subset of these interferon-induced genes, with some genes having specific effects on only one virus, and other genes having more broad effects on multiple viruses.

The researchers also showed that two genes in combination were more potent than either gene alone, supporting the long-standing hypothesis that many interferon-induced factors work in a combinatorial fashion. A number of the factors, the researchers found, work by interfering with the process by which viral RNA is translated in protein.

"It's fascinating that evolution has provided us with an array of hundreds of molecules that can be summoned by the host upon viral infection," says Schoggins. "Even more interesting is that none of these factors on their own are 'magic bullets' that can eradicate the virus. Instead, the cell relies on the cooperative action of numerous factors to effectively shut down the virus."

Schoggins and his colleagues hope their work will ultimately help inform the design of new antiviral drugs.

"This study is a first step toward unraveling how these previously uncharacterized, naturally occurring interferon-induced factors inhibit viruses," says Rice, who is the Maurice R. and Corinne P. Greenberg Professor at Rockefeller and scientific director of the Center for the Study of Hepatitis C. "In future studies, we hope to reveal the exact mechanisms by which these molecules suppress viral replication. If this can be done, then we will have a platform for the development of novel drugs that may be beneficial for combating viral infections."

**Journal Reference:**
John W. Schoggins, Sam J. Wilson, Maryline Panis, Mary Y. Murphy, Christopher T. Jones, Paul Bieniasz, Charles M. Rice. A diverse range of gene products are effectors of the type I interferon antiviral response. *Nature*, 2011; DOI: [10.1038/nature09907]

By Hannah Waters

**Overcoming resistance**
Altering microbial enzymes can lead to more powerful drugs that are effective against bacteria resistant to traditional antibiotics
[Published 11th April 2011 02:40 PM GMT]
The evolution of antibiotic-resistant bacteria has left researchers scrambling to develop new, stronger antibiotics. Now researchers have successfully used a method that may allow them to keep up -- manipulate the pathways used by microbes to produce the antibacterial products from which antibiotics are derived.

The researchers used the technique to create a powerful new antibiotic that is highly effective against vancomycin-resistant *Enterococcus* bacteria in vitro and in mice, according to the study published online on Sunday (April 10) in *Nature Chemical Biology*, and they are hopeful that it can be applied to other antibiotic systems.

"It seems to be very exciting -- we've found an activity against the resistance strains," said Stefano Donadio, the president of the antibiotic-developing company KtedoGen and Chief Scientific Officer of NAICONS who was not involved in the research. "But it's important to realize that it's just the beginning," he added. "There's still a long way to go before these can be of any benefit to human health."

Because glycopeptide antibiotics, such as vancomycin and teicoplanin, which work by inhibiting the ability of the bacterium to build cell walls, are toxic to human cells as well, they are only used as a last resort to fight bacterial infections. In the last five years, however, vancomycin use has gone up 79 percent, according to a recent study from the Veterans Healthcare Administration, increasing the chances that bacteria will evolve resistance to the drug. Indeed, there have been many reports of vancomycin resistance among common infectious bacteria, and even in methicillin-resistant *Staphylococcus aureus* (MRSA), one of the leading causes of hospital-acquired bacterial infections.

Tsung-Lin Li of Academia Sinica in Taiwan wondered if he could subtly alter the biochemical structure of glycopeptide antibiotics to boost their efficacy against the evolving bacteria. "If we
understand [antibiotic] biosynthesis, we maybe can make a hybrid or manipulate a gene," Li said. "Even the most modest structural modification can overcome the resistance."

Many antibiotics used today were originally isolated from soil microbes, such as fungi and bacteria, which use the compounds to protect themselves against competing microorganisms. Studying the bacterium *Nonomuraea* and its natural defense product, a glycopeptide antibiotic A40926, the researchers played with the molecular machinery responsible for the compound's production to see if they could alter its effectiveness against other bacteria.

They focused on an enzyme involved in the last step of A40926 synthesis, whose structure suggested that it could be easily manipulated. By providing different building blocks, the researchers could coax the enzyme to make slightly different variations of the antibacterial compound.

Testing the variations against vancomycin-resistant *Enterococcus* (VRE), a gram-positive bacterium similar to MRSA, the team identified a particularly promising candidate that worked better than vancomycin or teicoplanin at reducing bacterial cell counts *in vitro* and in the blood of VRE-infected mice.

"They really increased the activity on organisms that are otherwise resistant to teicoplanin and vancomycin," said Lynn Silver, an industry consultant at LL Silver Consulting who worked in antibacterial discovery for 21 years and was not involved in the research. Though whether or not the technique could be easily applied to other microbe-antibiotic systems also remains to be seen, she added. "What they've done is sort of specific, though the concept is not crazy."

It is also unclear how the antibiotics work, Donadio noted. "We don't know yet if these molecules they made act by the same or different mechanism of action than vancomycin or teicoplanin," he said. "It would have to be investigated if this compound would ever be tested in humans."


**News in a nutshell**

*By Megan Scudellari*

11 April 2011

This week’s news includes the spread of an antibiotic-resistant gene in microbes and international efforts to curb the rise of antibiotic resistance, the development of tiny kidneys from stem cells, the identification of the first patient in the Geron hESC trial, a 3D model of rat whiskers, and the genetic basis of caffeine fiends.

**Superbug spreading**

A gene conferring resistance to a major class of antibiotics appears to be spreading in bacteria. In August, researchers reported that infections involving New Delhi metallobeta-lactamase, or NMD-1, an enzyme which destroys a valuable class of antibiotics, were recorded in patients in Bangladesh, India, Pakistan and Britain. Now, a paper published last Thursday (April 7) in *Lancet Infectious Diseases* found NMD-1 present in bacteria in drinking water and sewage samples in New Delhi, India.

The spread of antibiotic-resistant genes across species of bacteria, including NMD-1, is causing a stir around the world. Last Thursday, World Health Day, the World Health Organization issued a call to action to combat the rise of antibiotic resistance, which they estimate currently costs the US health care system more than $20 billion and tens of thousands of lives lost each year. The Generating Antibiotic Incentives Now (GAIN) Act to incentivize the development of new antibiotics is expected to be introduced to the US Congress soon. India’s Union Health Ministry is also taking efforts to contain the spread of resistance in the form of a formal antibiotic policy to regulate the use of antibiotics in the country, according to *India Express*, though some infectious disease experts have questioned the ability of Indian officials to enforce stricter regulations, according to *The Telegraph* in Calcutta, India.

**Artificial kidney breakthrough**

Scientists at Edinburgh University in the UK have succeeded in creating an artificial mammalian kidney from stem cells. The kidney, which is half a centimeter in length, the size of a fetal kidney, was created using a combination of cells from human amniotic fluid and animal fetal cells, according to the *Daily Record*. The research is still ten years from the clinic, the team says, but they believe if the kidneys were
transplanted into humans, they would grow into a normal size, reports Stv.tv. If successfully taken to the market, the technology could dramatically reduce the demand for donor organs.

**First hESC therapy patient identified**
An Alabama nursing student paralyzed from the chest down after a car crash in September has come forward as the first patient in Geron’s human embryonic stem cell (hESC) trial for spinal cord injury, the first hESC trial approved in the United States. Timothy Atchison had more than 2 million cells derived from hESCs injected into his spine in September at the Shepherd Center in Atlanta. Atchison declined to discuss if the treatment had shown beneficial effects: “It’s too early to talk about that,” he told The Washington Post. “We’re just in the early stages right now. It’s not at the stage to really know what’s going on.”

By Patricia Bassereau and Bruno Goud

**The Movement of Goods Around the Cell**
A biologist and a physicist collaborate on a decade-long exploration of the physical parameters of membrane traffic in eukaryotic cells.

3-D reconstruction of confocal images showing membrane tubes pulled from a giant unilamellar vesicle by kinesin motors along microtubules. The tube diameter is about 100 nm and the vesicle diameter about 15 μm. Courtesy of Cécile Leduc

In prokaryotic cells, simple diffusion is largely responsible for getting nutrients to where they need to be and for removing waste products. But eukaryotes, which are much more complex, require a specialized mass-transit system. This system consists of membrane-bound structures called transport carriers that ferry cargo into, out of, and around the cell. Over the past decade, our interest has centered on this system, particularly on the interplay between the biophysical properties of the membranes and the way in which these properties are exploited by specific biological molecules to construct and direct this transport system. It is an ideal topic for collaboration between a biologist and a physicist.

When we were first introduced to one another in 2000 by Jacques Prost, who was then director of the physical chemistry lab at the Curie Institute, we could not have guessed that we’d become such close research collaborators, given our divergent interests and experience. Yet the encounter was no coincidence. The Institute was fostering links between cell biology and physics through a program called “Physics of the Cell” that allocated small cross-department grants. We quickly realized that the mechanisms behind the formation of transport carriers in cells excited us both, so we enthusiastically accepted the funding and started our collaboration.

One of us (Bruno) was an immunologist and cell biologist by training. Since 1986, Bruno has focused on Rab proteins, a family of small GTPases that regulate intracellular transport and membrane trafficking. The year before meeting Patricia, Bruno’s team, working with Ernst Stelzer’s group at the EMBL in Germany, had used microscopy to visualize the highly dynamic process that initiates the formation of membrane tubules and moves them along microtubules from the Golgi to the cell periphery. This novel transport pathway is controlled by Rab6, a Golgi-associated Rab.1
The other of us (Patricia) was trained as an experimental physicist in soft matter and had worked initially on the physical aspects of liquid crystals. The intrinsic nonequilibrium nature of biological membranes captured Patricia’s interest, leading her to study, in collaboration with Jacques Prost, the fluctuations of model lipid membranes in the presence of membrane proteins. Patricia had already known of Bruno’s findings on Rab6-decorated membrane tubules before we met.

**Assays and models**

Almost immediately, we agreed on our joint goal: we would develop an in vitro assay that mimics the initial steps of intracellular transport. In particular, we would concentrate on the creation of the tubular carriers and the membrane deformation involved in their formation. We recruited a student, Aurélien Roux, to work with us. Aurélien, who now has his own lab in the biochemistry department of the University of Geneva, would generate tubular carriers by attaching biotinylated kinesin motor proteins to biotinylated lipid membranes using 100-nm polystyrene beads coated with streptavidin. The membranes known as giant unilamellar vesicles (GUVs) provide a simplified model of a cell membrane lipid bilayer. (See figure 1, below.) When incubated with microtubules and ATP in small chambers, GUVs did indeed give rise to membrane tubes and to complex tubular networks that could be visualized by confocal microscopy. This experiment was the first demonstration that the force generated by kinesins was sufficient to pull a membrane tube from a membrane reservoir. Remarkably, as shown by transmission electron microscopy, the tubes that were pulled from GUVs made of egg phosphatidylcholine (EPC) had a constant diameter of 40±10 nm, a value close to that estimated for tubular transport carriers operating, for example, between the Golgi and the plasma membrane in vivo.

Membrane tubes similar to those involved in intracellular transport can be pulled by kinesin motor proteins bound to giant unilamellar vesicles (GUVs) that move along immobilized microtubules in the presence of ATP. The kinesins can be bound either via small streptavidin-coated polystyrene beads (left) or via streptavidin molecules associated with the lipid bilayer itself (right). Cristina Luiggi ( Courtesy of Bruno Goud)

A second student, Cécile Leduc, was able to monitor the dynamic accumulation of kinesins at the tips of membrane tubes, where the molecules are collectively responsible for generating sufficient force to form tubes. For these experiments, kinesins tagged with streptavidin were directly attached to the lipid membrane of GUVs via biotinylated lipids, following a method developed by the team of Marileen Dogterom in the Netherlands. (See figure 1.) In parallel, colleagues in the physics department had started to work on theoretical aspects of the physics of membrane tubes, to identify the forces and parameters involved in tube formation by molecular motors. Their analysis of the dynamics of motors on both vesicle and tube surfaces fitted Cécile’s experimental observations. Together, these studies identified the initial minimal surface density of motor proteins on the vesicle required to form membrane tubes, and, conversely, a maximum membrane tension above which motors cannot pull tubes. These model findings suggest that intracellular-membrane transport might be switched on and off in cells by regulating the number of available motors, the number of potential motor attachment sites (proteins or lipids) on the membrane, or the tension of the membrane. Cécile is now a researcher at the Centre de Physique Moleculaire Optique et Hertzienne in Bordeaux.

**Getting physical**

Using this minimal model, we also set out to investigate physical parameters involved in the early steps of intracellular transport, including membrane curvature, membrane bending rigidity, and membrane tension.

Because of the small diameter of actual transport carriers inside cells (typically 40–100 nm), they represent highly curved structures in comparison with the membrane from which they originate, which can be viewed as “flat.” During the early stages of vesicle formation from cell organelles, membrane proteins and lipids are sorted, ensuring efficient and accurate transport between cell compartments and the maintenance of homeostasis in organelle membranes. By 2004, the sorting of proteins had already been well described, but lipid sorting was much less clearly understood. To investigate constraints on lipid sorting, we pulled tubes from GUVs that were prepared from ternary mixtures of brain sphingomyelin,
cholesterol, and dioleoylphosphatidylcholine (DOPC), representing the three major lipid components of the external leaflet of the plasma membrane. Depending on the relative proportion of the three lipids, they either mix to form a single homogeneous phase, or they demix and preferentially segregate in different phases. In the latter case, two phases coexist, a liquid disordered phase enriched in DOPC, and a liquid ordered phase enriched in cholesterol and sphingomyelin. The disordered phase is so called because the lipid tails in these patches of membrane have kinks and are disorganized so they do not pack together as closely as in the ordered phase.

The force required to pull a tube is proportional to the bending rigidity and the tension of the membrane. Using optical tweezers coupled to a micropipette system, we measured the bending rigidity of the ordered and disordered phases. (See figure 2.) Membranes in ordered phase are about twice as rigid as membranes in the more loosely packed disordered phase. Given this, we predicted that lipids of the ordered phase should be excluded from tube formation, to reduce the energy cost needed to bend the membrane into tubes. This is exactly what we observed. In phase-separated vesicles, tubes were preferentially pulled out from the disordered phase; when pulled from homogeneous vesicles, the tubes were enriched in lipids of the disordered phase (DOPC). These experiments provided the first direct demonstration that lipid sorting can occur during the formation of highly curved membrane tubes. There are two hypotheses to explain lipid sorting during vesicle formation: either the vesicle is formed from domains of the donor membrane where the lipids are already segregated, or lipid sorting occurs at the same time as the vesicle forms. Our in vitro experiments support the latter hypothesis, namely the dynamic sorting of lipids.

General scheme of the experimental system used to study forces on a membrane. A membrane nanotube is pulled from a giant unilamellar vesicle (GUV) aspirated in a micropipette (left). A bead (orange sphere) trapped in an optical tweezers is attached to the GUV. The tube is formed by pulling the micropipette away from the GUV. At equilibrium, the force required to pull a tube is calculated from the bead displacement and from the tweezers' stiffness calibration.

To measure lipid sorting in a quantitative way, we jointly supervised another PhD student, Benoît Sorre, who is currently a postdoc at Rockefeller University in New York City. Benoît built a novel experimental arrangement that combined confocal microscopy, optical tweezers, and micropipette aspiration. Using force measurement and analysis of the redistribution of fluorescent lipids between tube and vesicle for GUVs of different lipid compositions, he was able to show that lipid sorting was effective only when the lipid composition of the GUV was near phase separation. He also found that lipid sorting was amplified in the presence of proteins that are able to cluster lipids, such as cholera toxin. Our theoretician colleagues developed a model based on membrane elasticity and nonideal solution theory (in which forces between the solution components are not equal) to explain Benoît's results. This model posits that the sorting of lipids between tube and vesicle is determined by a trade-off between mixing entropy and bending energy. The exclusion of lipids that have a tendency to form more rigid membranes lowers the energy required to form a curved membrane, and thus a thin tube. However, due to the small size of the lipid molecules, this effect is dominant over lipid mixing entropy only for compositions close to phase separation.

Lipid-manipulating proteins

Because the tool set available to biologists to study cellular function have been predominantly biochemical techniques, the story of how cells work is dominated by protein interactions. Recently, researchers have begun to appreciate that physical properties play a much bigger role in cellular activities than was previously suspected. In fact, it is the ways in which a cell takes advantage of physical and biochemical properties together that has interested us most.

Aurélien had also observed that when phase separation of lipids occurs in the tubes, fission events take place at the boundary between ordered and disordered domains. It turns out that these observations are consistent with a theoretical analysis in which membrane rupture was predicted to originate from the difference in surface energy between the two phases, caused by their different composition. Much as nonmiscible liquids minimize their surface of contact, the lipids in bidimensional lipid domains minimize the length of their contact, resulting in a constricting force called line tension. Since the lipids in cell
membranes are likely close to phase separation, these results raised the interesting prospect that the role of the numerous proteins implicated in sorting and fission events in vivo could be to trigger phase separation in membrane lipids, either by clustering specific lipids or by inducing membrane tubulation. Mechanoenzymes, including dynamin, are known to contribute to membrane fission. Dynamin is a large GTPase that polymerizes into a helical collar at the neck of endocytic buds, and induces the formation of endocytic vesicles through neck fission. Our work on line tension–induced membrane fission motivated us to explore the role of membrane curvature in the helical assembly of dynamin. Using a combination of confocal microscopy and optical tweezers, we discovered that membrane curvature triggers dynamin assembly, and thus the precise timing of the detachment of endocytic vesicles from the membrane.

The functions of proteins that sense or induce membrane curvature have received considerable attention recently because of the importance of these phenomena during the formation of vesicles and tubular carriers involved in intracellular transport. During formation, vesicles and tubules are surrounded by coat proteins, such as the COPI coatomer, which are recruited to the site by activated coat-recruitment proteins such as Arf1 (ADP-ribosylation factor), a small G protein that binds to Golgi membranes as the first step in coat assembly. Several proteins involved in vesicle formation, including the ArfGAP1 protein, contain a lipid-binding structural motif, named ALPS, that senses membrane curvature.

Proposed model for the association and dissociation of COPI coatomer in vivo. Coat proteins are recruited to the site of vesicle budding by membrane-bound Arf1 in its GTP form, and begin to deform the donor membrane. Sensing membrane curvature, ArfGAP1 is recruited to the budding site where it hydrolyzes GTP bound to Arf1, which then dissociates. As long as the budding site is attached to the donor membrane, the GTP form of Arf1 is replenished at the budding site. Once dissociated, the new vesicle lacks a fresh supply of Arf1-GTP. After all the Arf1-GTP has been hydrolyzed by ArfGAP1, the COPI coat dissociates from the newly formed transport vesicle or tubule.

The ALPS motif is a nonclassical amphipathic α-helix whose polar face, which interacts with lipid heads on the membrane surface, is enriched in serine and threonine residues rather than being composed of positively charged amino acids. This more hydrophobic nature likely explains the extreme sensitivity of proteins with ALPS motifs to membrane curvature. ArfGAP1 is a GTPase-activating protein (GAP) that stimulates the hydrolysis of GTP bound to Arf1. In its GTP conformation, Arf1 binds strongly to membranes, where it promotes the assembly of the COPI coat on the surface of transport vesicles operating between Golgi and ER. (See figure 3.) The rate of ArfGAP1–induced GTP hydrolysis is dramatically higher—by about 50 times—on Arf1 bound to small (highly curved) liposomes (35 nm) than on Arf1 bound to larger (flatter) liposomes (150 nm).

Our assay system was ideal for studying the spatial distribution of proteins between curved and noncurved membrane regions. Ernesto Ambroggio, a postdoc, worked with Benoît to compare the sensitivity to curvature of Arf1 and ArfGAP1. Arf1 bound almost equally well to the GUV membrane and to a tube pulled with kinesin motors or optical tweezers. Thus, Arf1 binding is, at most, only weakly sensitive to membrane curvature. In contrast, ArfGAP1 did not bind to the GUV at all. A curvature threshold was found for its binding to the membrane tubes: almost no binding was detected on tubes with a radius above 33±5 nm, while below this critical radius, ArfGAP1 density on the membrane increased linearly.
Gradient of Arf1 molecules (green fluorescent label) along a membrane tube containing lipids (red fluorescent label) pulled using a bead (large green sphere, right) trapped in an optical tweezers. The gradient is due to the competition between diffusion of Arf1-GTP from the giant unilamellar vesicle (GUV) on the left into the pulled membrane tube (green arrows) and the dissociation of Arf1-GDP induced by ArfGAP1 hydrolysis of Arf1-GTP, which occurs in the tube because of its high curvature. The low curvature of the GUV membrane prevents ArfGAP1 binding and protects Arf1-GTP from hydrolysis.

The next step towards understanding the influence of membrane curvature on ArfGAP1 enzymatic activity was to investigate the distribution of Arf1 on the vesicle and the membrane tube in the presence of ArfGAP1. ArfGAP1–induced GTP hydrolysis on Arf1 generated an Arf1 gradient along the tube, Arf1 density decreasing linearly from the base to the tip of the membrane tube. (See figure 4.) This nonuniform distribution of Arf1 along the tube was suggestive of a diffusion-dependent component to the reaction process: ArfGAP1 activity induces the dissociation of Arf1 from the tube; however, because the tube is connected to the vesicle (GUV), Arf1 can diffuse from the vesicle to the tube and compensate for Arf1 dissociation. This diffusion-reaction model has been experimentally validated. Taken together, these findings suggest that membrane fission is the triggering event for coat disassembly. When the neck of the COPI-coated vesicle is cut, the dissociation of Arf1 from the membrane after GTP hydrolysis is no longer compensated for by Arf1 diffusion. As a result, the coat should readily disassemble. (See figure 3.) Recently, Benoît has used a similar approach to study amphiphysin, a protein with a crescent-shaped binding domain that is involved in the generation of clathrin-coated vesicles. He showed that this protein has a dual behavior: at low concentration, its levels in membranes depend on membrane curvature—reminiscent of ArfGAP1—but it cannot deform the membrane. At high concentration, amphiphysin constricts a membrane tube, independently of the membrane tension (Sorre et al., submitted).

Perspectives

Our collaboration, combining biophysics and cell biology, and illuminated by our interactions with theoretical physicists, has been particularly fruitful and gratifying over the past 10 years. Right now we are planning to deepen our partnership still further with an ambitious project aimed at understanding how different classes of actin-based motors of the myosin family function in membrane trafficking and membrane dynamics. This project will exploit the minimal in vitro system developed in our laboratories. Over the last decade we have challenged one another and generated reciprocal interests: Bruno has become more receptive to and interested in physics concepts, and Patricia continues to explore projects more related to cell biology. Based on the results of our cross-disciplinary collaboration, we advise others to embrace the approach. The challenges and rewards of considering alternative perspectives will add exciting new dimensions to your research design and experimentation.

Patricia Bassereau and F1000 Member Bruno Goud are both at the Institut Curie in Paris. Bassereau leads the Membrane and Cell Functions group in the Physical Chemistry unit and Goud is the director of the Subcellular Structure and Cellular Dynamics unit where he leads the Molecular Mechanisms of Intracellular Transport group.

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Of course Africa is ready for PrEP!

April 12th, 2011

Whether or not Africa is ready for PrEP interests me because of several underlying assumptions in some of the answers about how we define Africa.

Africa’s MSM, Africa’s people who engage in anal sex and Africa’s public health prevention campaigns have been desperately in need of new HIV prevention options for a very long time. Issues of affordability can be strategically handled through diverse modalities. However, there is no doubt in my mind that access and availability remains burning questions at the heart of providing interventions to those who need it. Because there are many people in Africa who need HIV prevention, I say “Africa is ready for PrEP!”

It is important to recognise that there are many faces to Africa. There is the Africa which is poor, under-resourced, without cash reserves and unable to meet the costs of its survival. That’s the Africa in need of greatly subsidised if not entirely free interventions – be it lubes, gels, condoms or even PrEP. But there are also many African MSM who can afford PrEP. There are many MSM communities that can innovatively strategise through their local and international networks to find the resources to meet the costs of the drugs used for PrEP. There are many ways in which activism and negotiation with the powerful public organisations and actors can win unanticipated victories for providing access to PrEP to MSM who need it.

I have witnessed how innovative local LGBTI support groups and networks can be to access essential sexual health commodities in Kampala. I have observed “wealthier” MSM dispatching materials such as condoms, lubes and education pamphlets to those who cannot afford them or don’t have access to HIV prevention information. I have attended lobbying campaigns where small but significant successes were made to put MSM health onto the health and human rights agendas, particularly through arguing that it contribute to the fight against HIV/AIDS.

At the risk of sounding like a neoliberal capitalist who is blind to the needs of the less financially empowered in Africa, I think that current market trends in Kampala indicate that putting a product on the market, where there is both demand and need, results into the product being bought and used. And again, there is a need for PrEP in Africa.

The bigger question for me is, “Are the manufacturers of the ARVs used for PrEP (whether they are generics or the patented version) ready to meet the terms of the African clientele?” What are the possibility and the margins for negotiating the price of PrEP drugs? We could always argue that there is a sizeable market for PrEP in Africa because of relatively higher prevalence and incidence rates of HIV among those who engage in anal sex (whether MSM, MSW, WSM ...). Therefore there is economic sense in reducing the price of drugs in order to capture the African market. If the current price of drugs cannot be negotiated, is it possible to find innovative ways to ensure that Africa can meet the cost of providing PrEP to those who need it? Philanthropists, funding organisations, multi-lateral organisations, and the giants like the Global Fund for AIDS, Malaria and Tuberculosis can be engaged to consider making PrEP available to those who need it but cannot afford it.

Many of our public health systems in Africa are inadequately providing the essential services needed by the Poor in our communities and there are gaps in public health provisioning of mosquito nets, condoms, ARVs and many other essential health saving drugs and interventions. However this is no ground or rationale for claiming that Africa is not ready for another critically essential HIV prevention product.

It is important that we conduct meaningful acceptability trials of rectal microbicides and oral PrEP that have already shown sign of success in previous clinical trials, so that a wide range of people in Africa who practice anal sex can try and test them out. The feedback from these acceptability trials should be the basis upon which decisions about what form(s) of PrEP Africa is ready for are made.

At the micro level of individuals, people, lovers, sex partners, bodies who desire and consummate our passions anally, Africa is ready for PrEP. The macro issues of cost and affordability, acceptability, supply chains, rolling out and scaling up of PrEP interventions, can all be negotiated and strategically resolved.

Africa was ready for PrEP the day that Africa got HIV and AIDS. No question about it.
Editor’s Note:
The World Trade Organisation’s patent rules, known as Trade-Related Aspect of Intellectual Property Rights (TRIPS), recognise the right of countries to protect public health. They were introduced “in an attempt to narrow the gaps in the way [intellectual property] rights are protected around the world, and to bring them under common international rules”. The 2001 Doha declaration allowed flexibility in the application of TRIPS to ensure that medicines are available and affordable and that generic drugs can be produced and drugs imported at a lower cost than brand versions. Thailand and Brazil have both shown the way on how to use TRIPS to save life. Recently, the World Health Organization, the UN Development Programme, and UNAIDS agencies have encouraged the use of TRIPS to lower the cost of medicines

Distribution Of Cholera Vaccine To High-Risk Populations In Haiti Could Reduce Infections, Death, Study Says
Administering cholera vaccines to people in Haiti who live in high-risk areas could drive down the number of cholera infections and deaths in the country, according to a study published online Monday in the Proceedings of the National Academy of Sciences, Nature News reports. The study is the latest to weigh in on the impact such vaccination efforts could have on reducing the spread of the disease, which has sickened 274,418 people and led to the deaths of 4,787 in Haiti, according to the publication (Brower, 4/11).

"Using computer models that replicated the spread of the epidemic that began [in Haiti] last October,” researchers from Fred Hutchinson Cancer Center in Seattle, Washington, "simulated various proactive and reactive vaccination strategies,” according to a Fred Hutchinson Cancer Research Center press release (4/11).

According to the model, the researchers found "combined with basic public-health measures, vaccinating the 5% of Haitians most at risk of the disease would reduce the number of cholera cases by 11%. Vaccinating 30% of the population could cut cases by 55%, preventing 3,320 deaths,” the publication writes.

"What we are saying is embarrassingly simple,” lead author Dennis Chao, an epidemiologist at Fred Hutchison Cancer Center, said, adding, "If there is a limited amount of vaccine, obviously we should vaccinate people in areas with big numbers of the disease." However, "even vaccinating 5% of Haitians would require more doses – a million – than are currently available,” Nature News writes.

Researchers estimate there are roughly between 400,000 and 600,000 doses of oral cholera vaccines, study co-author Ira Longini, an epidemiologist at the University of Washington in Seattle, explained, adding that each vaccination requires two doses. The article describes how the global shortage of cholera vaccines has influenced the country’s response to the outbreak and the two available vaccines that currently exist – Dukoral, which has received approval by the WHO, and the lower-cost Shanchol, which is licensed in India, but "is still undergoing the WHO’s approval process."

"We believe there should be a comprehensive global plan for the use of cholera vaccine for epidemic cholera,” including the creation of "a large international mobile stockpile of oral cholera vaccine," the authors write in the study. "This stockpile should be large enough to vaccinate reactively 50-70% of the population at risk for high exposure in the affected country. ... Because both vaccines can be made relatively cheaply, current cost of about $5 U.S. for Dukoral and $1.50 U.S. for Shanchol, an international investment case could be made to support production and distribution of these vaccines," they write (Chao et al., 4/11).

According to Nature News, "[t]he International Vaccine Institute in Seoul is preparing a report for the WHO that will detail how many cholera vaccines should be stockpiled" (4/11).

Reuters Examines Growing HIV/AIDS Epidemic in Indonesia
Reuters examines the growing number of HIV/AIDS cases in Indonesia, where "widespread ignorance" about the disease and a government afraid of campaigning "effectively against it for fear of being accused by conservatives of promoting promiscuity" have helped fuel the epidemic. Currently, 300,000 Indonesians are HIV-positive, and though the nation’s HIV prevalence is low at 0.2 percent, "the government and health experts are worried because the number of newly confirmed cases has more than doubled to 4,158 in the five years to 2010." While other countries in the region are implementing high-profile prevention campaigns promoting condom use and needle-exchange programs, "such high-profile interventions cannot be adopted in conservative Indonesia," which is majority Muslim, Reuters reports (Lyn/Wulandari, 4/12). A factbox containing statistics on Indonesia’s HIV/AIDS epidemic is also available from Reuters (Lyn, 4/12).
PHILIPPINES: Condom prescription rules raise concerns
MANILA, 13 April 2011 (IRIN) - The growing number of villages seeking to outlaw the sale of condoms, birth control pills and other artificial forms of contraception without a prescription is worrying government officials and women’s rights groups.

Seven villages in Bataan, a low- to middle-income province west of the Philippine capital of Manila, are lobbying to enact a local ordinance to ban condoms and other forms of modern contraception without a prescription.

The ban comes on the heels of a similar ordinance passed in January 2011 in Ayala Alabang, one of the most affluent areas in the country.

"We feared that [the] Alabang [ordinance] would set a precedent and would only be the beginning. Alabang was never just a local issue, but one of national importance," Elizabeth Angsioco, head of the Democratic Socialist Women of the Philippines, told IRIN.

The Philippines is the only country in the Southeast Asian region without national legislation to institutionalize access to reproductive health information and services.

Delaying Reproductive Health Bill
Some say the recent legal moves are meant to distract from the bigger issue - the impending, highly contentious passage of the nation's first legislation on reproductive health (RH). Its provisions to make condoms and other forms of contraception readily available in hospitals have been debated for almost 20 years.

"We see these ordinances as the work of the anti-RH camp to deliberately thwart the passage of the RH Bill," said Ramon San Pascual, executive director of the Philippine Legislators’ Committee on Population and Development, a policy advocacy institution pushing for development policy reforms.

Recently, the RH Bill made significant progress. The current Aquino administration has openly stated its support for "responsible parenthood", unlike the previous administration, which promoted only natural family planning methods.

"If the national government doesn't put its foot down, they [anti-RH groups] will become bolder and pass similar ordinances. We cannot let our 42,000 villages impose their will, contrary to the interests of their constituents. We need the RH Bill to ensure access to reproductive health services and information for the poor, who need it the most," said former Department of Health Secretary Esperanza Cabral, who is also a resident of Ayala Alabang.

If the bill is passed, it will overrule all other local laws.

Condom use shamed
Condom use and contraception have always been a dilemma for this Catholic country of more than 100 million inhabitants. The Church has adamantly opposed any form of modern contraception, saying they are abortifacients that promote promiscuity. A strong social stigma surrounds condom use as a result.

"When I buy condoms at the drugstore, the cashier will look at me and I just know they're thinking I'm too young to be using the stuff," said Jet, a 22-year-old college student, who preferred anonymity.

The National Demographic Health Study of 2008, showed condom use at a mere 2.8 percent. Those surveyed preferred other methods, including unprotected withdrawal, at 9.8 percent.

As a result, the government of this lower-middle income country has been labouring to support a ballooning population with growth pegged at 2.04 percent, one of the highest in the region.

According to the National Statistics Coordination Board, 32.9 percent or 28 million Filipinos live on less than US$1 a day.

Constitutional questions
Government agencies have declared the proposed ordinances unconstitutional.

"A local council cannot regulate drugs and determine what’s safe and what’s not. Under the Food and Drugs Administration [FDA] Law, it is only the FDA who has the full powers to regulate food, drugs and other devices," said Pia Cayetano, head of the Senate Committee on Health and Demography.

However, in 2000, in Manila, an executive order was passed, declaring that only natural family planning methods would be promoted in government-owned hospitals and clinics. As a result, birth control pills, intrauterine devices and condoms are unavailable in government clinics and thus inaccessible to the poor. Under the same ordinance, which remains in effect today, vasectomies and tubal ligation are also illegal.

"We already saw this kind of religious bigotry before in the City of Manila," said Junice Melgar, executive director of the NGO Likhaan Women's Health Center. "We cannot let this happen again."

Supporters remain adamant that the RH Bill is not only necessary, but urgent.
"There are 11 mothers who die every day in the Philippines because of pregnancy-related deaths. That alone is enough reason to pass the RH Bill and make family planning accessible to all," said San Pascual of the Philippine Legislators' Committee on Population and Development.

**HIV Envelope Discovery Could Reveal New Vaccine Targets**

SUMMARY: Researchers have identified how the HIV envelope changes shape after binding to a host cell, exposing conserved proteins that might be good targets for a vaccine.

Below is an edited excerpt from a press release issued by the University of California at Davis describing the study and its findings.

**HIV Protein Unveils Vaccine Target**

March 30, 2011 -- An international study headed by a UC Davis scientist describes how a component of a potential HIV vaccine opens like a flower, undergoing one of the most dramatic protein rearrangements yet observed in nature. The finding could reveal new targets for vaccines to prevent HIV infection and AIDS. A paper describing the work was published online this week in the journal *Proceedings of the National Academy of Sciences*.

In the new study, researchers from the U.S., Sweden and France explored the structure and behavior of the HIV envelope protein complex, which could potentially serve as a component of a vaccine aimed at eliciting the human immune system to generate antibodies against HIV.

"By opening up these less exposed regions, we might be able to raise more broadly cross-reactive antibodies to HIV," said R. Holland Cheng, professor of molecular and cellular biology at UC Davis and senior author of the study.

HIV infects a type of white blood cell called the CD4 T-cell, weakening the immune system and leading to AIDS. HIV attaches to these cells through the envelope protein complex, which is made up of three gp120 proteins and three gp41 proteins, Cheng said.
First, the gp120 protein attaches to a CD4 protein on the victim cell's membrane. Then it uses gp41 to punch a hole through the membrane.

UC Davis graduate student Carlos Moscoso and project scientist Li Xing, working in Cheng's laboratory, used a cryoelectron microscope to study the structure of the complex and how it changes when it is exposed to a piece of the CD4 protein. A cryoelectron microscope derives three-dimensional images of complex protein structures from samples frozen in liquid nitrogen.

They found that when the HIV protein complex attaches to a CD4 protein, it rotates and flattens, exposing more of the gp41 proteins in the middle — probably allowing the gp41 protein to get closer to the cell membrane so it can lock on.

It also potentially exposes an area of the virus that would be vulnerable to attack by the immune system, Cheng said. If a person were vaccinated and had antibodies to such a protein region, they might be able to stop the virus at the point of invading the CD4 T cell.

The gp120 protein itself varies considerably between strains, so it has been difficult to make an effective vaccine against it. But these hidden protein regions vary less between different strains of HIV, Cheng said.

Cheng's group is part of the HIV Research and Design consortium formed by the National Institutes of Health to pursue new targets for HIV vaccines. In future work, the consortium plans to test potent antibodies from HIV-positive people who have survived without developing AIDS to see if the antibodies recognize the new potential vaccine targets.

Reference

Genital Viral Load Predicts Heterosexual HIV Transmission Risk

SUMMARY: Higher levels of HIV RNA in semen or female genital fluids are associated with a greater likelihood of HIV transmission during sex.

By Liz Highleyman
Prior research has shown that people with undetectable blood plasma HIV viral load have a lower risk of transmitting the virus to sexual partners or from mother to baby.

Plasma and genital fluid HIV RNA levels are related, but some individuals have detectable virus in their blood but not their genital fluids, or vice versa. However, the direct correlation between genital HIV levels and sexual transmission risk has not been well studied.

In the present study, described in the April 6, 2011, issue of Science Translational Medicine, Jared Baeten from the University of Washington and colleagues looked at the link between genital HIV RNA levels and transmission risk.

This prospective analysis included 2521 serodiscordant (1 HIV positive, the other negative) heterosexual couples in 7 African countries (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, and Zambia).

Participants underwent HIV testing and received prevention counseling every 3 months. The researchers tested cervical fluid swab samples from 1805 women and semen samples from 716 men. In cases of new HIV infection, viral sequencing was performed to determine if the initially negative member of a couple was infected by his or her steady partner.

Results

- 46 of the 1805 women tested transmitted HIV to their male partner.
- 32 of the 716 men tested transmitted the virus to their female partner.
- Overall, there was a positive correlation between genital fluid and plasma HIV RNA concentrations:
  - For cervical samples, Spearman's rank correlation coefficient -- a statistical measure of correlation -- was 0.56, indicating a strong relationship;
  - For semen samples, the coefficient was similar, at 0.55.
- Each 1 log increase in cervical fluid HIV RNA was associated with a 2.2-fold higher risk of
transmission.

- Each 1 log increase in semen viral load was associated with a 1.79-fold higher transmission risk.
- Genital fluid viral load still independently predicted HIV transmission risk after adjusting for plasma viral load (hazard ratio 1.67 for cervical fluid and 1.68 for semen).
- 7 cases of female-to-male transmission and 4 instances of male-to-female transmission occurred from people with undetectable genital fluid viral load, an incidence of <1% per year.
- In all 11 cases, however, the transmitted partner did have detectable plasma viral load.

Thus, the study authors concluded, "higher genital HIV-1 RNA concentrations are associated with greater risk of heterosexual HIV-1 transmission, and this effect was independent of plasma HIV-1 concentrations."

These data, they added, "suggest that HIV-1 RNA in genital secretions could be used as a marker of HIV-1 sexual transmission risk."

Although uncommon, however, the 11 cases of transmission with undetectable genital viral load indicate that plasma viral load is also an important consideration. 4/12/11

Reference

Injectable Gel Could Spell Relief for Arthritis Sufferers

ScienceDaily (Apr. 14, 2011) — Some 25 million people in the United States alone suffer from rheumatoid arthritis or its cousin osteoarthritis, diseases characterized by often debilitating pain in the joints. Now researchers at Brigham and Women’s Hospital (BWH) report an injectable gel that could spell the future for treating these diseases and others.

Among its advantages, the gel could allow the targeted release of medicine at an affected joint, and could dispense that medicine on demand in response to enzymes associated with arthritic flare-ups.

“We think that this platform could be useful for multiple medical applications including the localized treatment of cancer, ocular disease, and cardiovascular disease,” said Jeffrey Karp, leader of the research and co-director of the Center for Regenerative Therapeutics at BWH.

Karp will present the findings April 15 at the annual meeting of the Society for Biomaterials (SFB) as part of winning the coveted SFB Young Investigator Award for this work. The work was also reported by Karp and colleagues in the May 2011 issue of the Journal of Biomedical Materials Research (JBMR): Part A, and is currently available on the journal’s website.

Local Delivery

Researchers from Brigham and Women’s Hospital have developed a potentially new way to treat arthritis. Here their new gel (red, with yellow rectangles representing encapsulated medicine) is injected into an arthritic joint. There enzymes (black image) associated with arthritis break down the biodegradable gel, releasing the medicine. (Credit: Praveen Vemula, Karp lab, BWH)
Arthritis is a good example of a disease that attacks specific parts of the body. Conventional treatments for it, however, largely involve drugs taken orally. Not only do these take a while (often weeks) to exert their effects, they can have additional side effects. That is because the drug is dispersed throughout the body, not just at the affected joint. Further, high concentrations of the drug are necessary to deliver enough to the affected joint, which runs the risk of toxicity.

"There are many instances where we would like to deliver drugs to a specific location, but it’s very challenging to do so without encountering major barriers," says Karp, who also holds appointments through Harvard Medical School (HMS), Harvard Stem Cell Institute (HSCI), and the Harvard-MIT Division of Health Sciences and Technology (HST).

For example, you could inject a drug into the target area, but it won’t last long---only minutes to hours---because it is removed by the body’s highly efficient lymphatic system. What about implantable drug-delivery devices? Most of these are composed of stiff materials that in a dynamic environment like a joint can rub and cause inflammation on their own. Further, most of these devices release medicine continuously---even when it’s not needed. Arthritis, for example, occurs in cycles characterized by flare-ups then remission.

Toward the Holy Grail
"The Holy Grail of drug delivery is an autonomous system that [meters] the amount of drug released in response to a biological stimulus, ensuring that the drug is released only when needed at a therapeutically relevant concentration," Karp and colleagues write in JBMR. His coauthors are Praveen Kumar Vemula, Nathaniel Campbell, and Abdullah Syed of BWH, HMS and HSCI; Eric Boilard (now at Université Laval), Melaku Muluneh, and David Weitz of Harvard University; and David Lee of BWH, currently at Novartis. Karp notes the key involvement of Lee, a doctor who is "treating patients with the problem we’re trying to solve."

The researchers tackled the problem by first determining the key criteria for a successful locally administered arthritis treatment. In addition to having the ability to release drug on demand, for example, the delivery vehicle should be injectable through a small needle and allow high concentrations of the drug. The team ultimately determined that an injectable gel seemed most promising.

Next step: what would the gel be made of? To cut the time involved in bringing a new technology to market, the team focused only on materials already designated by the Food and Drug Administration as being generally recognized as safe (GRAS) for use in humans.

Ultimately, they discovered a GRAS material that could be coaxied into self-assembling into a drug-containing gel. "The beauty of self-assembly is that whatever exists in solution during the assembly process--in this case, a drug--becomes entrapped," says Vemula, first author of the paper, who also has an appointment at HST.

They further expected that the same material would disassemble, releasing its drug payload, when exposed to the enzymes present during inflammations like those associated with arthritis.

Promising Results
A series of experiments confirmed this. For example, the team created a gel containing a dye as a stand-in for a drug, then exposed it to enzymes associated with arthritis. The drug was released. Further, the addition of agents that inhibited the enzymes stopped the release, indicating that the gel "can release encapsulated agents in an on-demand manner," the researchers write. Although the team has yet to test this in humans, they did find that dye was also released in response to synovial fluid taken from arthritic human joints.

Among other promising results, the researchers found that gel injected into the healthy joints of mice remained stable for at least two months. Further, the gel withstood wear and tear representative of conditions in a moving joint.

Additional tests in mice are underway. The technique has yet to be demonstrated in humans, but the researchers write that it "should have broad implications for the localized treatment of many...diseases" caused by the enzymatic destruction of tissues. The researchers have applied for a patent on the work, which was sponsored by the Center for Integration of Medicine and Innovative Technology (CIMIT) through the U.S. Army and by the Harvard Catalyst Program.

Journal Reference:
Genital herpes more virulent in Africa than in US
BOSTON, Mass. (April 15, 2011) — Strains of genital herpes in Africa are far more virulent than those in the United States, researchers at Harvard Medical School report, a striking insight into a common disease with important implications for preventing HIV transmission in a region staggered by the HIV/AIDS epidemic. The researchers arrived at this finding by testing mouse model strains of the disease against vaccine candidates. All vaccines were far more efficacious in abating the U.S. strain.

The researchers say identification of the properties of the African viruses would open the door to developing a more potent vaccine against an infection now rampant in sub-Saharan Africa. This is important, they say, because genital herpes patients are more vulnerable to HIV/AIDS infection, as the open sores symptomatic of herpes contain a high concentration of immune cells that are targeted by HIV.

The challenge lies in formulating either a single vaccine that protects against both types of strains of the genital herpes virus or two different vaccines. The vaccine farthest along in development—it is headed for clinical trials in about a year—works best against the U.S. isolates of herpes simplex 2, but it also protects laboratory animals from the African viral strains if given in five-fold-higher doses.

This research, which appears online on April 15 in The Journal of Infectious Diseases, is led by David M. Knipe, the Higgins Professor of Microbiology and Molecular Genetics and vice chair of that department at Harvard Medical School, and Clyde Crumpacker, professor of medicine at Harvard Medical School and a physician in division of infectious disease at Beth Israel Deaconnes Medical Center. Their collaborators are former Knipe lab members Timothy E. Dudek, currently of the Ragon Institute of Massachusetts General Hospital, and Ernesto Torres-Lopez, now of the Universidad Autonoma in Monterrey, Mexico.

Live-virus vaccine
In southern Africa, infection rates among adults for genital herpes are exceedingly high— from 80 percent to 90 percent in some groups compared to slightly less than 20 percent in the United States.

In evolutionary terms, the herpes viruses are very old. They have honed their talents to become efficient parasites in humans, often persisting for decades while causing limited or no disease symptoms—although they can be deadly in immunocompromised persons and in newborns.

The herpes virus that causes ordinary cold sores, herpes simplex 1, is present in about 70 percent of the U.S. population. These stealthy viruses hide in nerve cells but can emerge over and over again, prompting repeated cold sore outbreaks.

Despite decades of research, there is no commercially available vaccine for herpes. But Knipe says their prototype vaccines are being tested in animals, and one such vaccine has been licensed to the French pharmaceutical firm Sanofi Pasteur.

According to Knipe, animal tests demonstrate clearly that the strains of herpes virus seen in sub-Saharan Africa are more virulent than the herpes simplex 2 virus strains seen in the United States. That difference suggests that an effective vaccine will probably have to be given to people in Africa in larger or more frequent doses. So far, says Knipe, results of animal tests are heartening.

Part of the promise in this work lies in the strong chance that a vaccine against herpes simplex 2 can help reduce the impact of HIV/AIDS in southern Africa. Epidemiological studies have shown that genital herpes infection is associated with a three-fold increase in the risk of HIV infection.

"If the rate of herpes infection can be reduced, it’s conceivable the rate of HIV/AIDS infection will also come down, perhaps reducing the death rate," says Knipe.

Knipe’s approach to vaccine development is based on using abnormal, live, mutant viruses to stimulate protective immune responses. These disabled viruses cannot multiply inside cells or cause symptomatic disease, but they do contain enough of the right proteins and molecules needed to arouse detection by a healthy immune system. Knipe’s strategy is to trigger a strong immune response without causing disease.

"The candidate vaccine, ACAM529, is under development by Sanofi Pasteur, and under the current plan will enter phase I clinical testing in 2012,” said Jim Tartaglia, a company representative. Phase I testing involves giving vaccine to a few human volunteers and watching for signs of toxicity. Trials for efficacy come later.

Although it has been difficult to create a vaccine for genital herpes, vaccines against a closely related herpes virus—varicella zoster virus, the cause of chicken pox and shingles—proved successful and are now widely used. This gives reason for optimism about a genital herpes vaccine.
The researchers do caution that, previously, two well-executed trials of Acyclovir, an effective, safe, antiviral drug for herpes, did decrease the occurrence of genital herpes infections but failed to prevent transmission of HIV-1 in African study participants.

**Forcibly sterilised if HIV-positive in Africa**

15 Apr 2011 02:41

Source: trustlaw // Tosin Sulaiman

By Tosin Sulaiman

LONDON (TrustLaw) - When Promise Mthembu went to a public hospital to have an abortion 14 years ago, the doctor told her he would terminate the pregnancy on one condition – she had to agree to be sterilised.

Mthembu, who is from Durban, South Africa, had been diagnosed with HIV two years earlier and she believes that was the reason behind the doctor’s ultimatum. Although she did not want to be sterilised, she felt she had no time to explore other choices and reluctantly agreed.

“It was explained to me but I felt as if it was coercion,” she told TrustLaw. “By law, I should be asking for sterilisation. It should not be offered to me as a condition.”

Mthembu, who already had a young daughter before undergoing the procedure, is still angry with the doctor. The sterilisation was done in such a way that it could not be reversed, she said, and her six attempts to conceive by IVF since then have failed. She said she takes anti-depressants from time to time.

“He possibly destroyed my life,” she said of the doctor. “After the operation I felt like hiding my face all the time. I felt I was not a full woman anymore because I could no longer reproduce.”

Mthembu has since discovered that her experience is not unique. Since January, the NGO she heads, Her Rights Initiative (HRI), has been collaborating with other partners to document cases of coerced sterilisation of HIV-positive women in South Africa. So far, Mthembu has interviewed 30 women from the province of KwaZulu-Natal who say they were forcibly sterilised, the majority at public hospitals. She said HRI is waiting for data from other provinces and that its legal partners are exploring the possibility of litigation.

The cases are not confined to South Africa. In nearby Namibia, eighteen HIV-positive women who allege they were sterilised at public hospitals without their informed consent have sued the government. The High Court of Namibia began hearing three of the cases in October 2009. The trial concluded in January and a judgment is expected later this year.

The International Community of Women Living with HIV/AIDS (ICW) began documenting the practice of forced and coerced sterilisation in 2008 after holding a series of workshops with HIV-positive women in Namibia. Of the 230 women ICW researchers interviewed at the workshops, 40 said they had been sterilised against their will, the organisation said in a report published in March 2009.

**Cases Of Consent Under Duress Or Lack Of Informed Consent**

In some of the cases, medical staff had failed to obtain consent from the women, who only found out they had been sterilised after the procedure had been carried out. Some women were asked to sign consent forms authorising sterilisation in order to access services, such as abortions, caesarean sections or assistance with the delivery of their babies, while others were presented with consent forms while they were in labour.

A number of women gave their consent based on misinformation, the report said. For example, they were told that their HIV status would put the lives of future children at risk. They were also misled about the risks of their child contracting HIV, said Aziza Ahmed, a former ICW legal fellow who conducted interviews with the women and co-authored the report.

“You are not giving true consent if the information is not full and accurate information about what you’re consenting to,” said Ahmed, who is now an assistant professor of law at Northeastern University in Boston. “In the U.S., for example, if you have full care delivered in the appropriate manner the chance that an HIV-positive woman will have a child with HIV is less than two percent. It’s very possible now for an HIV-positive woman to have a healthy child without HIV.”

Language barriers and the inability of many women to read or speak English also affected their treatment, ICW said. Many doctors in Namibia are foreign and do not speak local languages and hospitals often have no translators.

Ahmed said the women who were sterilised found the experience distressing, especially as their culture places a high value on motherhood. Those who hoped to get married worried about finding
husbands who would accept them, while those with partners feared being abandoned for women who could bear children.

**The Personal And Cultural Costs Of Forced Sterilisation**

“There are a whole set of consequences, from depression, the feeling of trauma, feeling frustrated with the medical system and there’s the reality of our world: in the Namibian context having a child is often conflated with womanhood,” she said.

Ahmed added that the sterilisations were happening in a much broader context of violations of the rights of HIV-positive women in the healthcare setting. According to UNAIDS, women account for more than half of all reported HIV infections in Namibia, where the HIV prevalence rate for adults is 15.3 percent.

“There’s a bias against HIV-positive women,” Ahmed said. “There’s a lot of discrimination that goes on (including) dissuading women from getting pregnant, not wanting to touch women while in labour, not giving adequate information about birth control.”

The 18 women who sued the Namibian government allege that they were sterilised because of their HIV status. Linda Dumba-Chicalu, a lawyer from the Legal Assistance Centre, which is representing the women, said they are from very poor backgrounds and have minimal education. Although they would like to have more children, IVF treatment is too expensive for them and is only available in South Africa. They are asking for compensation of 1 million Namibian dollars (approximately $150,000) each, but also want an opportunity to be heard in court, Dumba-Chicalu said.

“We’re asking the government to come up with a statement to say that there will be no more sterilisation of HIV-positive women without their informed consent,” she said.

Gladys Kamboo, a spokeswoman for the Namibian Ministry of Health and Social Services, said she could not comment as legal proceedings were still ongoing.

**US Meat and Poultry Is Widely Contaminated With Drug-Resistant Staph Bacteria, Study Finds**

ScienceDaily (Apr. 15, 2011) — Drug-resistant strains of *Staphylococcus aureus*, a bacteria linked to a wide range of human diseases, are present in meat and poultry from U.S. grocery stores at unexpectedly high rates, according to a nationwide study by the Translational Genomics Research Institute (TGen).

Nearly half of the meat and poultry samples -- 47 percent -- were contaminated with *S. aureus*, and more than half of those bacteria -- 52 percent -- were resistant to at least three classes of antibiotics, according to the study published April 15 in the journal *Clinical Infectious Diseases*.

This is the first national assessment of antibiotic resistant *S. aureus* in the U.S. food supply. And, DNA testing suggests that the food animals themselves were the major source of contamination.

Although Staph should be killed with proper cooking, it may still pose a risk to consumers through improper food handling and cross-contamination in the kitchen.

Researchers collected and analyzed 136 samples -- covering 80 brands -- of beef, chicken, pork and turkey from 26 retail grocery stores in five U.S. cities: Los Angeles, Chicago, Fort Lauderdale, Flagstaff and Washington, D.C.

"For the first time, we know how much of our meat and poultry is contaminated with antibiotic-resistant Staph, and it is substantial," said Lance B. Price, Ph.D., senior author of the study and Director of TGen’s Center for Food Microbiology and Environmental Health.

"The fact that drug-resistant *S. aureus* was so prevalent, and likely came from the food animals themselves, is troubling, and demands attention to how antibiotics are used in food-animal production today," Dr. Price said.

Densely-stocked industrial farms, where food animals are steadily fed low doses of antibiotics, are ideal breeding grounds for drug-resistant bacteria that move from animals to humans, the report says.

"Antibiotics are the most important drugs that we have to treat Staph infections; but when Staph are resistant to three, four, five or even nine different antibiotics -- like we saw in this study -- that leaves physicians few options," Dr. Price said.

"The emergence of antibiotic-resistant bacteria -- including Staph -- remains a major challenge in clinical medicine," said Paul S. Keim, Ph.D., Director of TGen’s Pathogen Genomics Division and Director of the Center for Microbial Genetics and Genomics at Northern Arizona University (NAU).

"This study shows that much of our meat and poultry is contaminated with multidrug-resistant Staph. Now we need to determine what this means in terms of risk to the consumer," said Dr. Keim, a co-author of the paper.
The U.S. government routinely surveys retail meat and poultry for four types of drug-resistant bacteria, but \textit{S. aureus} is not among them. The paper suggests that a more comprehensive inspection program is needed.

\textit{S. aureus} can cause a range of illnesses from minor skin infections to life-threatening diseases, such as pneumonia, endocarditis and sepsis.

The study was supported through a grant from The Pew Charitable Trusts as part of The Pew Campaign on Human Health and Industrial Farming.

**Countries Agree To Draft Framework On Virus Sharing, WHO Says**

After almost four years of negotiations, the WHO on Saturday announced it had reached an \textit{agreement} on sharing flu virus samples, \textit{Agence-France Presse} reports (4/17).

"Negotiators ended an all-night session with a draft agreement accepted by all countries, including the United States, the last to join the consensus, diplomats said," \textit{Reuters} writes (Nebeyay, 4/16). \textit{Intellectual Property Watch} describes some of the documents released last week during the working group session leading up to the final draft agreement Saturday (Saez, 4/15).

"The new framework includes certain binding legal regimes for WHO, national influenza laboratories around the world and industry partners in both developed and developing countries that will strengthen how the world responds more effectively with the next flu pandemic," according to a WHO \textit{press release}. "By making sure that the roles and obligations among key players are better established than in the past – including through the use of contracts – the framework will help increase and expedite access to essential vaccines, antivirals and diagnostic kits, especially for lower-income countries," the release states (4/17).

"The [pharmaceutical] industry has pledged to donate drugs and know-how, covering half of the $58 million (35 million pounds) annual cost of boosting defences in the poorest nations, according to senior envoys," Reuters continues. According to the news service, the International Federation of Pharmaceutical Manufacturers and Associations released a \textit{statement} supporting the plan (4/16).

"The framework provides a much more coherent and unified global approach for ensuring that influenza viruses are available to the WHO system for monitoring and development of critical benefits such as vaccines, antiviral drugs and scientific information while, at the same time, ensuring more equitable access to these benefits by developing countries," Keiji Fukuda, assistant director-general of Health Security and Environment at WHO, said, according to the WHO release (4/17). Health ministers will vote on the framework deal during the WHO's annual meeting in May, the \textit{Associated Press} reports (4/17).

"This has been a long journey to come to this agreement, but the end result is a very significant victory for public health," WHO Director-General Margaret Chan said, according to \textit{U.N. News Centre}. "It has reinforced my belief that global health in the 21st century hinges on bringing governments and key stakeholders like civil society and industry together to find solutions," Chan added (4/17).

**Zimbabwe: Patriarchy Slows Down Female Condom Use, Says Activist**

\textbf{Indiana Chirara}
16 April 2011

A prominent Aids activist has blamed culture for the slow uptake of the female condom in Zimbabwe. The female condom, which was first introduced in the country in 1997, has been touted as the best way of empowering women in sexual relationships.

Mary Sandasi, the Women and Aids Support Network director told journalists last week that Zimbabwean women were still not able to negotiate for safer sex because of their upbringing.

"The way a child is groomed has effects on their future," she said. "When a girl child is growing up she is taught to be submissive to her husband and boys grow up knowing they are more superior than girls.

"At the end of the day even those women who are well-resourced may not be in a position to negotiate for safer sex as they lack confidence."

Sandasi said age differences in many couples also made it difficult for women to initiate the use of female condoms.

"Campaigns and marketing of the product is vital," she said. "Training workshops for women are also of great importance for them to value themselves.

"It's time women learnt to protect themselves than to wait for men to protect them."

Patience Kunaka, the Population Services International (PSI) interpersonal communications manager said they had embarked on many initiatives to promote the use of female condoms.
"We have community outreach programmes where we are training hairdressers, barbers, church women and we are also working with sex workers at border posts and at growth points," Kunaka said.

But she said more work had to be done to reach all parts of the country but the efforts were being hindered by lack of funds. PSI has mainly been using hair salons to distribute the female condom.

**TIZ sees Global Fund repayment as proof of plunder**

By Misheck Wangwe and Sandra Lombe

Mon 18 Apr. 2011, 03:59

TRANSPARENCY International Zambia (TIZ) says it is an undisputed fact that President Banda’s administration is reluctant with the fight against corruption.

Commenting on the K9.1 billion which the government has paid to Global Fund as part of the refund of the money that was misappropriated by the Ministry of Health,

TIZ executive director Goodwill Lungu said it was unfortunate that taxpayers’ money was being looted and nothing tangible was being done to correct the situation.

Lungu said it was practically impossible for the government to avoid making a refund to the Global Fund because it was clear that there was rampant abuse of donor funds.

He said the repayments the government was making to Global Fund had spoken volumes on the rampant abuse of both public and donor funds taking place in government.

Lungu said the people of Zambia expected President Banda’s government to demonstrate true commitment to fighting corruption by putting in place mechanisms to stop the rampant abuse of public funds.

“We all know that there are a number of government officials who had stolen public funds. We know that some of these officials are still walking the streets of Lusaka as if they are free. We expect the culprits to be brought to book so that it serves as a big lesson to would-be offenders,” Lungu said.

He said it was disheartening that many people had died in the country because money for medicines was being stolen by disgruntled public officers in the Ministry of Health and other government departments.

Lungu said the country would not see meaningful development in important sectors such as health if pragmatic steps were not taken to stop the abuse of funds by the government.

“There must be a vigorous campaign against fraud in the health and other sectors. The repayments government is making to the Global Fund must be a big lesson for this country. It is sad that with limited and hard-earned resources, we are paying back billions of kwacha because of corruption,” Lungu said.

He said President Banda and his ministers must be able to realise that by paying huge sums of money to Global Fund, the fight against corruption in his government had to a great extent dwindled.

The Zambian government has agreed to make the repayment of Global Funds money which was misappropriated by the Ministry of Health in three installments.

It has since transferred K9.1 billion into the Global Fund account as the first installment.

According to the Global Fund, the principal recipients in Zambia misappropriated US $13 million, which the government had been ordered to pay back.

And Women and Law in Southern Africa regional coordinator Matrine Chuulu said government should always be accountable and not only when issues involving misuse of funds came up before the public.

“We have been critical on Global Fund misuse by the health sector and its impact on the service delivery. First it (the refunding) is an indicator that something went wrong and they are taking responsibility. It’s accountability they should have admitted,” she said.

Chuulu said the government should have taken steps long ago to stop pilfering in the health sector.

**Can Lowering Community Viral Load Decrease New HIV Infections?**

**SUMMARY:** Decreased average and maximum community viral load (CVL) was associated with a decline in new HIV infections in San Francisco, and new HIV diagnoses are decreasing along with CVL in New York City, but this correlation has not yet been observed in Washington, DC, researchers reported at CROI 2011.

By Liz Highleyman

Starting antiretroviral therapy (ART) earlier appears beneficial for HIV positive individuals, but the public health effects of expanding treatment are not yet fully understood and remain a subject of controversy.

People on effective combination ART usually have low or undetectable viral load, and lower viral load dramatically reduces the likelihood of transmitting the virus during sex or injection drug use.
The recent 18th Conference on Retroviruses and Opportunistic Infections (CROI 2011) in Boston featured a poster discussion session devoted to community viral load -- or the average viral load in a population -- and its effects on local HIV/AIDS epidemics.

"Community viral load is an attempt to monitor the health of a community as individual viral load does for an individual," moderator Susan Buchbinder from the San Francisco Department of Public Health (DPH) said at a CROI press conference discussing the findings.

**San Francisco**

Moupali Das from the San Francisco DPH and colleagues used active case surveillance data from San Francisco's comprehensive HIV/AIDS case registry to assess trends in mean CD4 cell count at diagnosis, ART initiation, viral load, and time to virological suppression.

San Francisco has one of the most aggressive programs of HIV testing and linkage to care among U.S. cities. As previously reported, San Francisco General Hospital and the DPH last year adopted a policy of offering ART to everyone diagnosed with HIV, regardless of CD4 T-cell count.

The researchers estimated community viral load in 4 ways: the averages of the most recent, minimum, and maximum viral load for all cases in the past year, and log transformation of the mean of the most recent viral load. They then assessed the relationship of these CVL measures and newly diagnosed and reported HIV cases.

HIV positive people in San Francisco are generally diagnosed early compared with other cities. The mean CD4 count at the time of diagnosis remained consistently > 400 cells/mm³, while mean CD4 count at the time of ART initiation increased from about 350 to nearly 450 cells/mm³ between 2007 and 2009.

Das said there were "dramatic improvement in all markers" during the study period. Most recent, minimum, and maximum CVL all declined significantly between 2004 to 2009, and were significantly associated with decreases in the number of both newly diagnosed and newly reported HIV cases.

The most recent average CVL fell from about 25,000 copies/mL in 2004 to about 10,000 copies/mL in 2009, while the number of new HIV diagnoses decreased from 820 to 500 during the same period. Furthermore, the time from HIV diagnosis to virological suppression decreased from 32 months in 2004 to 5 months in 2009, with time from ART initiation to viral suppression falling from about 19 months in 2004 to 3 months in 2009.

Based on these findings, the researchers concluded, "Since 2004 and substantially in the last year, there have been notable gains in San Francisco's efforts to offer individuals earlier treatment and reduce time to virologic suppression, which has been associated with reductions in the community viral load and correlates with decreased newly diagnosed and newly reported HIV cases."

Das attributed these changes to expanded HIV testing, more frequent testing, and more formalized linkage to care programs, as well as "tremendous gains" in ART effectiveness during this time period that have enabled viral suppression in people who were not previously suppressed.

**New York**

Fabienne Laraque and colleagues from the New York City Department of Health and Mental Hygiene evaluated community viral load as a population-level marker to monitor the impact of interventions to control HIV.

This analysis included HIV positive city residents reported to the NYC HIV Registry who were alive at the end of 2008 and had at least 1 viral load measurement reported as of December 31, 2009. CVL was defined as the mean of individual viral load averages reported between January and December 2008.

New York City's CVL in 2008 was approximately 20,000 copies/mL overall, and approached 45,000 copies/mL among people with detectable viral load (> 400 copies/mL). But CVL varied significantly according to demographic characteristics, clinical characteristics, and neighborhood. Men, young and middle-aged adults, men who have sex with men, people with AIDS, individuals with low CD4 count, and people diagnosed after 2006 had higher mean viral loads.

Overall, about 55% of HIV positive people achieved virological suppression, again varying widely according to individual and neighborhood characteristics. Whites and Asians and people older than 30 years were more likely to have undetectable viral load.

"Community viral load can be utilized to target interventions aimed at groups and neighborhoods with higher community viral load and to track the impact of HIV control interventions," the investigators concluded.

CVL is a useful public health outcome measure, but can be politically tricky, Laraque said at the CROI press conference. "We must target [people who most need care] but not point fingers," she emphasized. "The positive spin is that there's something we can do."

**Washington, DC**
Finally, Amanda Castel from George Washington University School of Public Health and Health Services and colleagues assessed trends in CVL in Washington, DC, which has one of the highest HIV/AIDS rates in the U.S. The researchers analyzed data on all prevalent HIV/AIDS cases diagnosed and reported to the DC HIV/AIDS surveillance database between 2004 and 2008. The most recent viral load for each individual was used to calculate average and total CVL.

About half of the more than 15,500 people diagnosed with HIV/AIDS between 2004 and 2008 had at least 1 available viral load measurement. The average CVL among this subset using the most recent viral load was nearly 56,000 copies/mL, while the total CVL was more than 422,000,000 copies/mL. During the 5-year study period, total CVL significantly increased, but mean CVL significantly declined. To date, however, this has not been associated with falling HIV incidence.

The average of the most recent viral load measurements was highest for women, blacks, and people infected via heterosexual sex, injection drug use, or "other" modes of transmission. The highest mean CVL was observed in areas with the highest levels of poverty and unemployment, and the lowest proportion of high school graduates.

"Mean and total community viral load, as markers of access to care and treatment, and indicators of the viral burden in the population, are useful in assessing trends in local HIV/AIDS epidemics," the researchers concluded. "This methodology may serve as a novel tool for assessing the potential impact of HIV prevention interventions at a population level."

References

Universal Testing and Treatment Could Reduce New HIV Infections by 76%

A growing body of evidence suggests that HIV positive individuals may benefit from starting antiretroviral therapy (ART) sooner than recommended by current U.S. guidelines.

More controversial is a strategy of starting everyone on treatment as soon as they are diagnosed, regardless of CD4 T-cell count. People on combination ART typically have low or undetectable viral load. Reducing an individual's viral load lowers the risk of HIV transmission, and reducing the average community viral load may decrease the rate of new infections. San Francisco General Hospital (SFGH) and the San Francisco Department of Public Health adopted this approach last year.

As described in the April 15, 2011 issue of Clinical Infectious Diseases, researchers from SFGH, the Department of Public Health, and the University of California at San Francisco's Center for AIDS Prevention Studies produced mathematical models to predict how expanded ART and HIV testing might influence incidence rates among men who have sex with men, who account for most new infections in San Francisco.

Below is an edited excerpt from a press release issued by UCSF describing the research and its findings. HIV Rate in SF Could Be Cut Sharply with Expanded Treatment, Study Predicts

If HIV-infected adults in San Francisco began taking antiretroviral treatments as soon as they were diagnosed, the rate of new HIV infections among men who have sex with men would be cut by almost 60 percent over five years, according to a new study by scientists at the University of California, San Francisco.

In San Francisco, men who have sex with men comprise more than three quarters of the population of people living with HIV and more than three quarters of new HIV infections occur in this group. The study looked specifically at the impact of treatment upon rates of new HIV infections in this population.

The finding is published in the April 15, 2011 issue of Clinical Infectious Diseases.
The decision of when to begin treatment with antiretroviral drugs is a subject of some debate, with the experts evenly split on whether to begin antiretroviral therapy immediately upon HIV diagnosis or waiting until a patient's CD4 cell count drops below 500 cells per microliter.

Early last year, the UCSF Division of HIV/AIDS at San Francisco General became the first clinical practice in the country to recommend treatment upon diagnosis to all of its HIV-infected patients. The San Francisco Department of Public Health followed suit shortly thereafter. The two programs combined treat about a third of the HIV-infected patient population in San Francisco.

"San Francisco has been successful in promoting HIV testing for individuals at risk and in getting infected persons into care and effective treatment," said study lead investigator, Edwin D. Charlebois, MPH, PhD, associate professor of medicine at the UCSF Center for AIDS Prevention Studies. "In this study, we sought to estimate what the outcomes of different strategies including immediate and universal treatment would be on the rate of new infections -- the community level HIV prevention effect."

"Recent evidence suggests that, in addition to benefiting the individual, HIV treatment can reduce the likelihood of HIV transmission to other persons. We found that, just by changing the strategy of when to start treatment in individuals already in care, our model predicts significant reductions in new HIV infections among men who have sex with men in San Francisco."

In addition, the study found that adding annual HIV testing for men who have sex with men in the city to universal treatment could bring the reduction in new infections down by 75 percent, the researchers report in their paper. "Our findings show that we can obtain even greater reductions in new HIV infections if we do a better job of encouraging people to get tested, continue to improve our linkages to care and offer treatment to all HIV patients," said study co-author, Diane V. Havlir, MD, chief of the UCSF Division of HIV/AIDS at San Francisco General Hospital.

Researchers modeled three expanded antiretroviral treatment scenarios in San Francisco: one being the current standard of care where treatment is offered to HIV-infected patients with CD4 cell counts below 500, the second offering treatment to all HIV patients receiving care and the third strategy combining intensified annual HIV testing for men who have sex with men with treatment for all HIV-infected patients.

The model predicts that the implementation of the third strategy -- a full "test and treat" approach -- in San Francisco would cut in half the percentage of men who have sex with men living with HIV in the city from its current level of about one in four to one in eight in twenty years.

"Our clinicians recommended initiating antiretroviral therapy to all of our HIV positive patients based on our assessment that delaying treatment allows the virus to do damage to major organs systems and would lead to poorer outcomes for patients. It is too early to tell if this shift in treatment strategy last year by our clinic and the Department of Public Health has had any impact in preventing HIV infections," said Havlir.

"Notwithstanding the community benefit from reduced rates of new infections -- which we view as an added gain -- we strongly believe that the primary reason HIV patients should start antiretroviral therapy upon diagnosis is so that they will experience better health and will have a longer life span than if they had waited," she added. 4/19/11

Reference

Closer Look at Cell Membrane Shows Cholesterol 'Keeping Order'
Cell membranes form the "skin" of most every cell in your body, but the ability to view them up close and in motion cannot be rendered by many experimental techniques. A team of scientists working at the National Institute of Standards and Technology (NIST) and University of California, Irvine, recently developed a way to magnify them dramatically. Their work has helped illuminate the important role of cholesterol within this boundary between the cell and the outside world.

The multi-institutional team used tools at the NIST Center for Neutron Research (NCNR) to examine the membrane at more than 1,000 times the resolution offered by an optical microscope -- the equivalent of magnifying the point of a needle to the size of a large building. This enabled an unprecedented look at the membrane, which -- because it controls access to our cells -- is a major target for many drugs.

"Drugs that affect pain sensation, heart rhythm, mood, appetite and memory all target proteins lodged in the cell membrane that function like little gates," says Ella Mihailescu of the Institute for Bioscience and Biotechnology Research, a joint institute of NIST and the University of Maryland. "Because membranes and their proteins are important to medicine, we would like a better picture of how the membrane functions -- and not just a better snapshot. We want to see it move, as it does constantly in real life."

Optical microscopes offer limited resolution, while the more powerful electron microscopes require freezing samples before they can be magnified. But by using neutron diffraction, which does not require frozen subjects, the team not only observed the membrane more closely and in motion, but they also gained insight into the long-known phenomenon of the membrane growing thicker and stiffer in the presence of cholesterol.

These lipid chains form a two-layer skin with the "heads" of the lipids facing outward toward the cell's exterior and interior and the "tails" intermingling on the inside of the cellular membrane. Cholesterol is known to be important for managing disorder in membranes. The team saw for the first time that when cholesterol is present, these tails line up in a tight formation, looking like a narrow stripe from which the lipid chains stretch outward -- and producing the order that had been previously anticipated, but never
shown directly. But without cholesterol, the tails go a bit wild, flapping around energetically and in some cases even pushing up toward their chains' heads.

Mihailescu says the findings hint that cholesterol may have profound consequences for the membrane's gatekeeper proteins, which are very sensitive to their environment. "The membrane and its proteins interact constantly, so we're curious to learn more," she says. "With this unique magnification technique, we can explore the cell membrane more effectively than ever possible, and we are now establishing a research program with the University of Maryland to do so in greater detail."

**Journal Reference:**

**Common Virus Plus Low Sunlight Exposure May Increase Risk of Multiple Sclerosis**
ScienceDaily (Apr. 19, 2011) — New research suggests that people who are exposed to low levels of sunlight coupled with a history of having a common virus known as mononucleosis may be at greater odds of developing multiple sclerosis (MS) than those without the virus. The research is published in the April 19, 2011, print issue of Neurology®, the medical journal of the American Academy of Neurology.

"MS is more common at higher latitudes, farther away from the equator," said George C. Ebers, MD, with the University of Oxford in the United Kingdom and a member of the American Academy of Neurology. "Since the disease has been linked to environmental factors such as low levels of sun exposure and a history of infectious mononucleosis, we wanted to see whether the two together would help explain the variance in the disease across the United Kingdom."

Infectious mononucleosis is a disease caused by the Epstein-Barr virus, which is a Herpes virus that is extremely common but causes no symptoms in most people. However, when a person contracts the virus as a teenager or adult, it often leads to infectious mononucleosis. The body makes vitamin D when exposed to ultraviolet B (UVB) light.

For the study, researchers looked at all hospital admissions to National Health Service hospitals in England over seven years. Specifically, they identified 56,681 cases of multiple sclerosis and 14,621 cases of infectious mononucleosis. Scientists also looked at NASA data on ultraviolet intensity in England.

The study found that adding the effects of sunlight exposure and mononucleosis together explained 72 percent of the variance in the occurrence of MS across the United Kingdom. Sunlight exposure alone accounted for 61 percent of the variance.

"It's possible that vitamin D deficiency may lead to an abnormal response to the Epstein-Barr virus," Ebers said.

He noted that low sunlight exposure in the spring was most strongly associated with MS risk. "Lower levels of UVB in the spring season correspond with peak risk of MS by birth month. More research should be done on whether increasing UVB exposure or using vitamin D supplements and possible treatments or vaccines for the Epstein-Barr virus could lead to fewer cases of MS."

**Journal Reference:**

**Gold-based drug shows promise in clearing HIV reservoir in monkey study**
Keith Alcorn
Published: 20 April 2011
A gold-based drug already used for treatment of rheumatoid arthritis significantly reduced the reservoir of viral DNA and the population of long-lived HIV-infected memory CD4+ cells in a study conducted in six monkeys, Italian and American researchers report in the journal AIDS.

However the decrease in viral DNA was transient in animals that received three-drug antiretroviral therapy, and was sustained only in those that received an intensified antiretroviral regimen alongside the gold-based drug auranofin.

Reduction of the number of cells containing integrated HIV DNA is likely to be an essential step in achieving a functional cure for HIV infection. A functional cure is usually defined as a reduction in the reservoir of HIV-infected cells that allows HIV treatment to be stopped without viral rebound.

So far, no cure for HIV infection has been achieved except in the most challenging circumstances.

However more researchers are becoming optimistic about the prospects for a cure for HIV infection, and the International AIDS Society has launched an international working group to develop a Global Scientific Strategy that will speed up research in this area.
The Italian study used a drug called auranofin, a gold-based oral drug used to treat rheumatoid arthritis. One effect of this drug is to decrease the pool of central memory T-lymphocytes without affecting the body’s ability to generate new T-lymphocytes. It also shortens the lifespan of newly generated T-cells, limiting the replenishment of the reservoir.

Central memory CD4+ T-cells may live for many years. This group of cells is infected by HIV, and forms a very long-lasting reservoir of HIV in the body of every infected person.

As soon as treatment is halted, the reservoir of HIV DNA integrated into these cells begins to fuel viral replication once more, eventually resulting in a rebound of HIV to pre-treatment levels. Previous attempts to cure HIV infection using intensive antiretroviral therapy have always run up against this barrier.

A treatment which could remove these cells and limit the production of new cells for a period, alongside antiretroviral therapy, might have potential for achieving a functional cure.

Auranofin’s effect on the HIV reservoir was tested in six macaques infected with SIV, a simian equivalent of HIV. The animals had been treated with an antiretroviral regimen of tenofovir, FTC and raltegravir and had had undetectable viral load for at least eight weeks.

They were treated with 1.5mg/kg twice daily for one week, and received 2mg/kg per twice daily thereafter, along with antiretroviral therapy.

Auranofin treatment resulted in:

- Shortening of the lifespan of the longest-lived CD4+ T-cells after one month, and reduction in the size of this population;
- No effect on the size of the naïve T-cell population;
- Stable CD4+ T-cell counts
- No change in undetectable plasma viral load;
- A significant reduction in SIV DNA, to below the limits of detection for four weeks in animals treated with three-drug ART, followed by a rebound, but persistent undetectability to eleven weeks in animals that received an ART regimen intensified with darunavir boosted with ritonavir.

Six animals treated with intensified ART also received two three-day cycles of vorinostat at week 10. Vorinostat is an HDAC inhibitor, a type of drug which can stimulate HIV or SIV replication from cells in which the virus is lying dormant. No rebound in viral load occurred in these animals, but in two control animals that did not receive auranofin, viral load rebounded after one cycle, suggesting that in the intensively treated animals the viral reservoir had been substantially depleted.

The researchers also tested what happened when all treatment was removed. In control animals treated only with intensified ART virus levels rebounded after an average of 1.5 weeks to pre-therapy levels. In comparison animals treated with auranofin showed viral rebound to levels significantly lower than before treatment in most cases, and this took 7-8 weeks.

One macaque still had very low viral load seven months after the treatment was stopped, and a stable CD4 count. In other cases CD4 counts declined very little after viral rebound.

The research was carried out by Dr Andrea Savarino and colleagues at the Istituto Superiore di Sanità in Rome.

“As the side effects of this approach in the presence of HIV are as yet largely unexplored”, Dr. Savarino warned in a press release, “I strongly recommend that people living with HIV/AIDS do not buy the drug from uncontrolled sources such as e-Bay and start self-treatment outside highly medicalised settings.”

The authors of the study have decided to wait a little before moving to clinical trials. “We prefer not to involve people in a trial of the drug immediately”, said Dr. Enrico Garaci, president of the Italian Institute of Health, and co-author of the study, “that’s because in this phase the trial could only be a proof-of-concept study, and we have already this proof in monkeys. We prefer to put all our effort in the intensification of the attack on the virus reservoir in monkeys by using a combined approach”. “This will also allow”, he adds, “a more thorough evaluation of the safety of the approach”.

Reference
Lewis MG et al. Gold drug auranofin restricts the viral reservoir in the monkey AIDS model and induces containment of viral load following ART suspension. AIDS, advance online publication, April 20, 2011. (View free abstract here).

HIV study claims one in eight children resistant to drugs
First major study of young people with HIV questions the suitability of anti-retroviral drugs for young sufferers

Drugs for use in HIV treatment. A study warns that anti-retrovirals may not be suitable for young patients. Photograph: David Gray/REUTERS
One in eight children born with HIV becomes resistant to the three main classes of drugs used to suppress the virus within five years of starting treatment.

The first major study of drug resistance in young people, which looked at 1,000 European children born with HIV, raises questions about the suitability of anti-retroviral drugs for the young.

Drugs fail because the virus becomes resistant to them. This can happen if people take them erratically or stop taking them. Resistance sets in with adults, but more slowly.

But part of the problem, say Nathan Ford and Alexandra Calmy, is that the drugs available are not tested on children or turned into formulations that are easy for children to take. The doctors work for Médecins sans Frontières, which treats some of the 2 million children living with HIV, who were infected during childbirth – most of them in the developing world. Half of the children born with HIV die before their second birthday, they point out.

Even in the US and Europe, drugs for children with HIV are limited. "Of the 22 antiretroviral drugs currently approved by the US food and drug administration, five are not approved for use in children and six are not available in paediatric formulations," they write in a commentary published with the study in the Lancet medical journal.

"Additionally, treatment has to be constantly adjusted for bodyweight, and most paediatric antiretrovirals are formulated as syrups (often in large volumes) which are difficult to administer and store." Some of the drugs, they add, "are extremely unpalatable".

Half of the children born with HIV already die before their second birthday, they point out. To give more children a chance of staying alive, fixed-dose combinations of a three-drug cocktail are needed, in tablet form. They call on "drug developers, clinical trial investigators and drug regulators" to prioritise the production of better HIV drugs for children.

The study was carried out mostly in the UK, Ireland, Spain, the Netherlands and France, with smaller numbers also from Denmark, Italy and Belgium. The children were all younger than 16 and had started treatment with three or more drugs between 1998 and 2008.

The failure rate in the three main classes of drugs – known as nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs), non-NRTIs (NNRTIs), and protease inhibitors – was 12% within five years of starting. There were problems even with young children, where the parent or carer would be responsible for giving the medicine, but the failure rate was higher in older children.

"Drug adherence is a challenge for children and young people with any chronic disease. For those with HIV infection, there are additional factors, including coming to terms with disclosure of their HIV status, secrecy and guilt among adult family members and dealing with HIV alongside their own sexual development. Fear of stigma increases their isolation and tendency towards denial, all of which might adversely affect drug adherence."

Swaziland: No Money For AIDS But The King's OK
Richard Rooney
20 April 2011

Swaziland — While AIDS groups are forced to close because their funds have been cut, money is flowing at an increasing rate to King Mswati III and his royal family.

News emerged yesterday (19 April 2011) that groups set up to help Swaziland people living with HIV and AIDS are about to close because they are no longer getting financial support, even though Swaziland's HIV rate of 26.1 percent is the highest in the world.

A report from IRIN said that one AIDS group, the Swaziland AIDS Support Organisation (SASO), was about to close due to lack of funds. The report said 600,000 people in a population in Swaziland of roughly one million had benefited from community outreach programmes run by SASO, or support organizations SASO has helped organize.

SASO is about to grind to a halt. Previous financial benefactors, including the Swazi Government, have had to cut back or eliminate their assistance in the wake of economic meltdown in Swaziland.

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Last week, the Swaziland National Network of People Living with HIV and AIDS (SWANNEPHA), the umbrella body with which SASO works closely, announced at a press conference that it was also facing imminent closure if new sources of funding were not found.

SWANNEPHA receives its funding from the Global Fund to fight AIDS, Tuberculosis and Malaria, via Swaziland’s National Emergency Response Council on HIV and AIDS (NERCHA). SWANNEPHA had its budget reduced from US$130,000 (E882,000) in 2008 to $100,000 in 2009.
But, while money cannot be found to keep the HIV AIDS support groups going, the same cannot be said about money for King Mswati, sub-Saharan Africa’s last absolute monarch.

In February this year (2011) the budget for King Mswati and the royal household was raised by E40 million (US$5.88 million) for the coming year. By comparison the US$130,000 for SWANNEPHA is a drop in the ocean.

But it doesn’t end there. This is for the second consecutive year that the budget for King Mswati Royal increased by E40 million - in the 2010/11 financial year, the royal budget went from E130 million to E170 million.

The greed of King Mswati and the royal family seems to know no bounds. The Nation magazine reported this month (April 2011) that the King's office spent about E13 million ($1. 8 million) on internal decor for three of the royal guest houses.

Taurai Maduna/IRIN

King Mswati - one of Africa’s last executive monarchs - is being blamed for the current financial crisis.

The decor include furniture, curtains, carpet, wood floor and cladding, bathrooms, artwork and accessories, sound system, multi media system, TV, phones and water meters.

On top of this, E125 million a year is regularly allocated for the rehabilitation, maintenance and construction of state houses. And E25 million is available for link roads to royal residences.

Yesterday was the King’s 43rd birthday and next week is the 25th anniversary of his victory in a power struggle within Swaziland that saw him crowned king.

You might therefore be pleased to know that the budget for the Celebrations Office is E12.5 million – roughly 14 times the annual budget of SWANNEPHA.

**What’s your gut type?**

**Gut bacteria could help with diagnostics and influence treatments**

In the future, when you walk into a doctor's surgery or hospital, you could be asked not just about your allergies and blood group, but also about your gut type. Scientists at the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany, and collaborators in the international MetaHIT consortium, have found that humans have 3 different gut types. The study, published today in Nature, also uncovers microbial genetic markers that are related to traits like age, gender and body mass index. These bacterial genes could one day be used to help diagnose and predict outcomes for diseases like colo-rectal cancer, while information about a person's gut type could help inform treatment.

We all have bacteria in our gut that help digest food, break down toxins, produce some vitamins and essential amino acids, and form a barrier against invaders. But the composition of that microbial community – the relative numbers of different kinds of bacteria – varies from person to person.

"We found that the combination of microbes in the human intestine isn’t random," says Peer Bork, who led the study at EMBL: "our gut flora can settle into three different types of community – three different ecosystems, if you like."

Bork and colleagues first used stool samples to analyse the gut bacteria of 39 individuals from three different continents (Europe, Asia and America), and later extended the study to an extra 85 people from Denmark and 154 from America. They found that all these cases could be divided into three groups, based on which species of bacteria occurred in high numbers in their gut: each person could be said to have one of three gut types, or enterotypes.

The scientists don't yet know why people have these different gut types, but speculate that they could be related to differences in how their immune systems distinguish between 'friendly' and harmful bacteria, or to different ways of releasing hydrogen waste from cells.

Like blood groups, these gut types are independent of traits like age, gender, nationality and body mass index. But the scientists did find for example, that the guts of older people appear to have more
microbial genes involved in breaking down carbohydrates than those of youngsters, possibly because as we age we become less efficient at processing those nutrients, so in order to survive in the human gut, bacteria have to take up the task.

"The fact that there are bacterial genes associated with traits like age and weight indicates that there may also be markers for traits like obesity or diseases like colo-rectal cancer," Bork says, "which could have implications for diagnosis and prognosis."

If this proves to be the case, when diagnosing or assessing the likelihood of a patient contracting a particular disease, doctors could look for clues not only in the patient's body but also in the bacteria that live in it. And after diagnosis, treatment could be adapted to the patient's gut type to ensure the best results.

**How TRIM5 fights HIV**

Thanks to a certain protein, rhesus monkeys are resistant to HIV. Known as TRIM5, the protein prevents the HI virus from multiplying once it has entered the cell. Researchers from the universities of Geneva and Zurich have now discovered the protein's mechanism, as they report in *Nature*. This also opens up new prospects for fighting HIV in humans.

Unlike people, certain monkey species, such as rhesus or night monkeys, are resistant to HIV thanks to TRIM5, a cellular protein: In the case of an HIV infection, the protein intercepts the virus as soon as it enters the cell and prevents it from multiplying. We have known about TRIM5 for over six years. However, the mechanism TRIM5 uses to prevent the HI virus from multiplying was still largely unknown.

The majority of the key aspects of TRIM5's defense mechanism against HIV was discovered by the Swiss research teams of Prof. Jeremy Luban, University of Geneva, and Prof. Markus Grütter, University of Zurich, in collaboration with teams from the USA and France. They demonstrated that TRIM5 immediately triggers an immune response if infected with HIV. Consequently, TRIM5 is an HIV sensor in the innate immune system. Unlike the adaptive immune system, which only develops when confronted with a pathogen, the innate immune system is already able to eliminate pathogens as soon as it comes into contact with them.

The HI virus, which penetrates the cell during an infection, has a shell, the components of which are arranged in a lattice, similar to the pattern on a soccer ball. TRIM5 recognizes this lattice structure and specifically attaches itself to it. This stimulates the protein to produce signal molecules known as polyubiquitin chains in the cell. These chains immediately trigger an anti-viral reaction. The "alerted" cell can then start eliminating cells infected with HIV by releasing messenger substances (cytokines).

Humans also have a TRIM5 protein, but it is less effective in fending off HIV. However, the findings in resistant monkeys have opened up new possibilities and ways of fighting HIV in humans. 33 million people are currently infected with HIV worldwide; two million die of AIDS each year. And with 2.7 million people becoming infected every year, HIV remains a major problem.

**Ends of Chromosomes Protected by Stacked, Coiled DNA Caps, Penn Study Finds**

Implications for studying human aging, Werner syndrome, and Bloom syndrome

PHILADELPHIA - Researchers at the University of Pennsylvania School of Medicine are delving into the details of the complex structure at the ends of chromosomes. Recent work, *e-published in Nature Structural & Molecular Biology* last month, describes how these structures, called telomeres, can be protected by caps made up of specialized proteins and stacks of DNA called G-quadruplexes, or "G4 DNA." Telomere caps are like a knot at the end of each chromosome “string,” with the knot's role preventing the string from unraveling.
"Although G4 DNA has been studied in test tubes for years, we did not know whether it could contribute to telomere protection in actual cells until we performed our studies in yeast cells," stated **F. Brad Johnson, MD, PhD**, associate professor of Pathology and Laboratory Medicine.

complex and unusual, involving a DNA sequence with guanine building blocks that loop back and forth on top of each other to form a four-stranded stack, which is different from the two-stranded arrangement of typical DNA molecules. The stack protects the chromosome from unraveling by specialized enzymes.

The length of telomeres is associated with age. Shortened telomeres are observed in aging cells and in some rare syndromes. There is mounting evidence that loss of telomere capping may contribute to some diseases that become more common with natural aging. An example of extreme aging associated with telomere defects is Werner syndrome, a rare genetic disease in which individuals develop normally until puberty. After this they age rapidly, so that by age 40 or so they often appear several decades older. The protein missing in people with Werner syndrome but present in healthy people, is a helicase, an enzyme that unzips DNA. A slightly different G4-unwinding helicase is missing in people with a related disease, called Bloom syndrome, which is characterized by chromosome instability and high rates of cancer. It's possible that changes in G4 DNA contribute to the symptoms of these two syndromes.

The normal unwinding of DNA is critical under many particular circumstances, for example during replication. There are hundreds of different types DNA helicases in human cells, and each unwinds DNA under different circumstances. Although it is important to keep the strands of DNA together most of the time, if they can’t be unwound when needed, serious problems could occur.

The Penn researchers hope to eventually explore the role of G4 capping in human aging after they know more about the G4 cap in yeast cells, which are easy to study because they can be engineered to make very specific changes in their DNA and proteins.

Recently, Johnson’s group found that DNA sequences with the potential to form G4 DNA, which exist not only at telomeres but also at many locations throughout the entire human genome, are closely connected to changes in gene expression in cells from people with Werner or Bloom syndrome. They predict that G4 DNA abnormalities also exist at the telomeres in these human diseases and perhaps those of aging cells.

In their experiments in which telomeres were specifically examined in yeast, both elevated levels of G4 binding protein and inactivation of the yeast helicase that is similar to the one missing in human Werner and Bloom syndrome patients led to increased protection of the telomeres. This suggested that the G4 caps were present on the telomeres and that they protected the telomere from breaking down.

The overall role of G4 DNA is not simple and might seem to be contradictory. For example, work from several other research groups has suggested that G4 DNA can interfere with the replication and capping of telomeres, in contrast to the protective role observed by Johnson’s group.

"This points out the complexity of G4 DNA," said Johnson. "On one hand, some G4 DNA may help cap telomeres, but too much G4 DNA or formation of G4 DNA at the wrong times or places may be detrimental. G4 DNA is not a single thing, but is rather a family of related structures, and so it might be possible to target particular types of G4 DNA to, for example, improve telomere capping in normal cells or disrupt the growth of cancer cells. This is a very new field, and it will be fun to see how far it might go."

**Antibiotics Cure Anthrax in Animal Models**

ScienceDaily (Apr. 19, 2011) — In the absence of early antibiotic treatment, respiratory anthrax is fatal. The 2001 bioterrorism attacks in the US killed four people, out of 22 infected (10 of them with respiratory anthrax), despite massive antibiotic administration, probably because therapy did not begin until the disease had reached the fulminant stage. But a multi-agent prophylaxis initiated within 24 hours post-infection prevented development of fatal anthrax respiratory disease, and treatment combining antibiotics with immunization with a protective antigen-based vaccine conferred long-term protective immunity against reestablishment of the disease, according to a study in the April 2011 issue of the journal *Antimicrobial Agents and Chemotherapy*. This study is the first to characterize the severity of respiratory anthrax that can be cured.
The researchers, all from the Israel Institute for Biological Research, Ness-Ziona, tested both the efficiency of different therapeutic approaches in preventing fatal disease from developing in infected animals, and their ability to cure animals in which the disease had developed into a systemic, septic phase. Rescue remains possible with appropriate agents even if initiated two days after infection.

Treatment initiated 24 hours after infection with any of four antibiotics protected the animals during treatment, but many of the animals died of anthrax after treatment was stopped, the antibiotics conferring degrees of protection ranging from 10-90 percent. Combining antibiotic treatment with a protective antigen vaccine left all animals fully protected even after the end of treatment.

Animals whose treatment was delayed beyond 24 hours post-infection developed varying degrees of bacteremia and toxemia. Treatment with doxycycline cured both sick guinea pigs and rabbits exhibiting low to moderate bacteremia; adding protective antigen vaccine to the mix boosted the level of bacteremia that was curable 10-fold in the guinea pigs and 20-fold in the rabbits. But ciprofloxacin plus a monoclonal anti-protective antigen antibody was still more effective.

In all cases, the surviving animals developed immunity against anthrax via subcutaneous challenge.

"Our results suggest that doxycycline and ciprofloxacin are efficient antibiotics to treat anthrax, not only as post-exposure prophylaxis, but also during the systemic phase of the disease," the researchers write. "Treatment with both antibiotics can cure guinea pigs and rabbits in an advanced stage of systemic anthrax"

Journal Reference:

NYTimes, April 20, 2011

**Bacteria Divide People Into 3 Types, Scientists Say**

By CARL ZIMMER

In the early 1900s, scientists discovered that each person belonged to one of four blood types. Now they have discovered a new way to classify humanity: by bacteria. Each human being is host to thousands of different species of microbes. Yet a group of scientists now report just three distinct ecosystems in the guts of people they have studied.

**Blood type, meet bug type**

"It’s an important advance," said Rob Knight, a biologist at the University of Colorado, who was not involved in the research. "It’s the first indication that human gut ecosystems may fall into distinct types."

The researchers, led by Peer Bork of the European Molecular Biology Laboratory in Heidelberg, Germany, found no link between what they called enterotypes and the ethnic background of the European, American and Japanese subjects they studied.

Nor could they find a connection to sex, weight, health or age. They are now exploring other explanations. One possibility is that the guts, or intestines, of infants are randomly colonized by different pioneering species of microbes.

The microbes alter the gut so that only certain species can follow them. Whatever the cause of the different enterotypes, they may end up having discrete effects on people’s health. Gut microbes aid in food digestion and synthesize vitamins, using enzymes our own cells cannot make.

Dr. Bork and his colleagues have found that each of the types makes a unique balance of these enzymes. Enterotype 1 produces more enzymes for making vitamin B7 (also known as biotin), for example, and Enterotype 2 more enzymes for vitamin B1 (thiamine).

The discovery of the blood types A, B, AB and O had a major effect on how doctors practice medicine. They could limit the chances that a patient’s body would reject a blood transfusion by making sure the donated blood was of a matching type. The discovery of enterotypes could someday lead to medical applications of its own, but they would be far down the road.

"Some things are pretty obvious already," Dr. Bork said. Doctors might be able to tailor diets or drug prescriptions to suit people’s enterotypes, for example.

Dr. Bork notes that more testing is necessary. Researchers will need to search for enterotypes in people from African, Chinese and other ethnic origins. He also notes that so far, all the subjects come...
from industrial nations, and thus eat similar foods. “This is a shortcoming,” he said. “We don’t have remote villages.”

The discovery of enterotypes follows on years of work mapping the diversity of microbes in the human body — the human microbiome, as it is known. The difficulty of the task has been staggering. Each person shelters about 10 trillion microbes.

(For comparison, the human body is made up of only around 10 trillion cells.) But scientists cannot rear a vast majority of these bacteria in their labs to identify them and learn their characteristics.

As genetics developed, scientists learned how to study the microbiome by analyzing its DNA. Scientists extracted DNA fragments from people’s skin, saliva and stool. They learned how to recognize and discard human DNA, so that they were left with genes from the microbiome. They searched through the remaining DNA for all the variants of a specific gene and compared them with known species. In some cases, the variants proved to be from familiar bacteria, like E. coli. In other cases, the gene belonged to a species new to science.

These studies offered glimpses of a diversity akin to a rain forest’s. Different regions of the body were home to different combinations of species. From one person to another, scientists found more tremendous variety. Many of the species that lived in one person’s mouth, for example, were missing from another’s.

Scientists wondered if deeper studies would reveal a unity to human microbiomes. Over the past few years, researchers have identified the genomes — the complete catalog of genes — of hundreds of microbe species that live in humans. Now they can compare any gene they find with these reference genomes.

They can identify the gene’s function, and identify which genus of bacteria the microbe belongs to. And by tallying all the genes they find, the scientists can estimate how abundant each type of bacteria is.

In the recent work, Dr. Bork and his team carried out an analysis of the gut microbes in 22 people from Denmark, France, Italy and Spain. Some of their subjects were healthy, while others were obese or suffered from intestinal disorders like Crohn’s disease. Dr. Bork and his colleagues searched for fragments of DNA corresponding to the genomes of 1,511 different species of bacteria. The researchers combined their results with previous studies of 13 Japanese individuals and 4 Americans.

Scientists then searched for patterns. “We didn’t have any hypothesis,” Dr. Bork said. “Anything that came out would be new.”

Still, Dr. Bork was startled by the result of the study: all the microbiomes fell neatly into three distinct groups.

And, as Dr. Bork and his colleagues reported on Wednesday in the journal Nature, each of the three enterotypes was composed of a different balance of species. People with type 1, for example, had high levels of bacteria called Bacteroides. In type 2, on the other hand, Bacteroides were relatively rare, while the genus Prevotella was unusually common.

“You can cut the data in lots of different ways, and you still get these three clusters,” Dr. Bork said.

Dr. Bork and his colleagues found confirmation of the three enterotypes when they turned to other microbiome surveys, and the groups continue to hold up now that they have expanded their own study to 400 people.

**Starting HIV treatment when CD4 cell count dips below 500 improves AIDS-free survival**

Michael Carter
 Published: 21 April 2011

Patients who start antiretroviral therapy when their CD4 cell count dipped below 500 cells/mm³ are less likely to develop an AIDS-defining illness than individuals who start treatment with a CD4 cell count of 350 cells/mm³, an international team of investigators report in the *Annals of Internal Medicine*.

However, initiating HIV treatment with a CD4 cell count of approximately 500 cells/mm³ did not reduce the risk of all-cause mortality.

“If the goal is to prevent AIDS-defining illness or death, our findings support cART [combination antiretroviral therapy] initiation once the CD4 cell count decreases below 500 cells/mm³,” comment the investigators.

Importantly, the investigators did not gather information on the impact of earlier treatment on the risk of serious, but non-fatal, non-AIDS related illnesses.
The authors of an accompanying editorial suggest that the results of the study should be treated with “caution,” and that doctors should have “frank conversations with their patients about what we do and what we don’t know about starting cART.”

Nevertheless, results of the study will undoubtedly inform the debate about the best time to start antiretroviral therapy.

Treatment guidelines in Europe currently recommend that AIDS-free patients should start therapy when their CD4 cell count is in the region of 350 cells/mm³. However, US guidelines advocate treatment when an individual’s CD4 cell count falls under 500 cells/mm³.

Large randomised trials are currently underway to try and determine the optimum time to start HIV therapy. However, their results are not expected for several years. Because of this continuing uncertainty investigators from the HIV-CAUSAL Collaboration undertook a prospective observational study involving approximately 21,000 adult patients enrolled in cohorts in Europe and the US.

All the patients had a CD4 cell count above 500 cells/mm³ when they entered the study, and none had developed an AIDS-defining illness. The patients were recruited between 1996 and 2009. At the time of entry to the study, the patients had a median CD4 cell count of 660 cells/mm³.

The risk of all cause mortality and the risk of AIDS-related illness or death was compared between patients who started HIV treatment when their CD4 cell count was 500 cells/mm³ or above; between 350-499 cells/mm³; 200-349 cells/mm³; and below 200 cells/mm³.

A total of 390 patients developed an AIDS-defining illness or died before their CD4 cell count fell below 500 cells/mm³. HIV therapy was started by 2893 patients when their CD4 cell count was above 500 cells/mm³, and 9296 maintained a CD4 cell count above this level without the need for treatment.

The remaining 8292 patients experienced a fall in their CD4 cell count to below 500 cells/mm³ after a median of nine months.

There was no evidence that starting HIV therapy at CD4 cell counts around 500 cells/mm³, or 350 cells/mm³ significantly reduced the risk of all-cause mortality compared to initiating treatment at a CD4 cell count of 200 cells/mm³. This was equally low for all patients.

However, there was clear evidence that starting therapy at higher CD4 cell counts reduced the risk of AIDS-related illnesses or death.

Compared to patients who started treatment when their CD4 cell count fell below 500 cells/mm³, individuals initiating therapy when their CD4 cell count was below 350 cells/mm³ were 38% more likely to develop AIDS (hazard ratio [HR], 1.38; 95% CI, 1.23-1.56). Furthermore, patients who first took therapy when their CD4 cell count was below 200 cells/mm³ were 90% more likely to develop an AIDS-defining illness (HR = 1.90; 95% CI, 1.67-2.15).

Five-year survival rates were 98% for patients with a CD4 cell count around 500 cells/mm³, 98% for patients with a CD4 cell count around 350 cells/mm³ and 97% for individuals with a CD4 cell count of approximately 200 cells/mm³. AIDS-free survival rates were 92%, 92% and 88% respectively.

The investigators calculated that “approximately 48 patients would need to initiate cART when their CD4 cell count decreased below 500 cells/mm³ rather than 350 cells/mm³ to prevent 1 new case of AIDS-defining illness or death during the first 5 years.”

They add, “however, we estimated little change in all-cause mortality rates between the 500-350 threshold.”

Heart, kidney, and liver disease are now important causes of illness among people with HIV. The investigators acknowledge that a limitation of their study was lack of information on “serious nonfatal events other than AIDS-defining illnesses.”

The authors of the accompanying editorial comment that the study “is a robust, carefully performed analysis that supports the presence of a graded benefit of cART even when the risk for AIDS is low.”

However, they add, “the continuing HIV epidemic and tightening of resources requires that we clarify the absolute benefits, risks and costs of expanding the indications for cART.”

Reference
2. Baker JV et al. If we can’t get what we want, can we get what we need? Optimizing use of antiretroviral therapy in the current era. Annals of Internal Medicine, 154: 563-65, 2011.
Research suggests that men who have difficulty maintaining an erection when they use condoms are (unsurprisingly) less likely to use them consistently and more likely to have unprotected sex. The solution may be to build a better condom.

As the WSJ reports, a contraceptive aimed at helping men maintain their erections — developed by U.K. biotech Futura Medical and licensed to the maker of Durex condoms, the brand now owned by consumer-products company Reckitt Benckiser — is nearing approval in Europe. The medical purpose: to cut down on the risk of sexually-transmitted diseases (such as HIV, seen at right).

It’s not clear whether the manufacturer plans to apply to the FDA to market the product here, but the agency would certainly require more data reflecting U.S. patients.

The condom is lined with a gel containing a vasodilator that increases blood flow to the penis and so helps maintain erections. Futura came up with a way to deliver the drug in a formulation that wouldn’t weaken the condom and would “immobilize” the drug in the lubricant so it would only affect the wearer, the WSJ says.

While the product has been compared to Pfizer’s Viagra in condom form, that’s not exactly accurate since it’s intended not for men with erectile dysfunction in general, but those who specifically have difficulties keeping an erection when using a condom.

The experimental condom is not-so-catchily called CSD500; Reckitt will no doubt come up with something better if the product is approved.

**WHO Updates Numbers On Measles Outbreak In Europe**

The WHO on Thursday released updated figures on the measles outbreak in Europe that has reached more than 6,500 cases in 33 countries, with close to 5,000 reported in France, the Associated Press reports. Britain, Germany, Netherlands, Norway, Romania, Russia, Spain and Switzerland also have reported cases and worsening outbreaks, the news service writes (4/21). CNN’s "The Chart" blog says resistance from some Europeans to receiving the measles, mumps, rubella (MMR) vaccine could be contributing to the outbreaks (4/20).

**Subset of self-destructive immune cells may selectively drive diabetes**

New research identifies a distinctive population of immune cells that may play a key role in the pathogenesis of diabetes. The research, published by Cell Press and available online in the April 21st issue of Immunity, sheds new light on the pathogenesis of diabetes and may lead to the development of new more selective therapeutic strategies for diabetes and other autoimmune diseases of the accessory organs of the digestive system.

Type 1 diabetes (T1D) is a chronic autoimmune disease that develops when the immune system destroys insulin-producing cells in the pancreas. Previous work using a mouse model of diabetes (nonobese diabetic or "NOD" mice) demonstrated that multiple types of immune cells are necessary for the development of T1D, including two different types of T cells, CD4+ and CD8+ T cells, as well as B cells. The individual roles and interactions of these cells in the pathogenesis of T1D are not well understood.

"We do know that the cytokine interleukin (IL)-21 is produced by CD4+ T cells and plays a critical role in autoimmune diseases, and that IL-21 contributes to the proliferation, differentiation and survival of motile types of immune cells," explains senior study author, Dr. Cecile King from the Garvan Institute of Medical Research. "However, how IL-21 mediates its effect on autoimmune disease pathogenesis remains an important unanswered question."

Dr. King and colleagues discovered a subset of CD4+ T cells that produce IL-21 and that express a protein called chemokine receptor 9 (CCR9). In healthy humans, CCR9 is found primarily in T cells that selectively migrate to the gut and is thought to play a role in several inflammatory disorders of the gastrointestinal tract. The researchers showed that this newly identified subset of CD4+ cells also infiltrate the pancreas and other accessory organs of the digestive system and "help" CD8+ cells to elicit T1D.

"We identified a subset of CD4+ T cells that may contribute to the regional specification of organ-specific autoimmune disease," concludes Dr. King. "Recent studies have demonstrated that IL-21 is critical for the maintenance of CD8+ T cells during chronic infection. In our study we showed that IL-21 is also important for the survival of diabetogenic CD8+ T cells. Further studies are needed to confirm that this population of cells is necessary for autoimmune diseases that afflict accessory organs of the digestive system and to explore the possibility that targeting this cell population as a potential therapeutic strategy for diabetes."
Caltech: Learning to tolerate our microbial self

PASADENA, Calif.—The human gut is filled with 100 trillion symbiotic bacteria—ten times more microbial cells than our own cells—representing close to one thousand different species. "And yet, if you were to eat a piece of chicken with just a few Salmonella, your immune system would mount a potent inflammatory response," says Sarkis K. Mazmanian, assistant professor of biology at the California Institute of Technology (Caltech).

Salmonella and its pathogenic bacterial kin don’t look that much different from the legion of bacteria in our gut that we blissfully ignore, which raises the question: What decides whether we react or don’t? Researchers have pondered this paradox for decades.

In the case of a common “friendly” gut bacterium, Bacteroides fragilis, Mazmanian and his colleagues have figured out the surprising answer: "The decision is not made by us," he says. "It’s made by the bacteria. Since we are their home, they hold the key to our immune system."

What’s more, the bacteria enforce their "decision" by hijacking cells of the immune system, say Mazmanian and his colleagues, who have figured out the mechanism by which the bacteria accomplish this feat—and revealed an explanation for how the immune system distinguishes between beneficial and pathogenic organisms.

In addition, the work, described in the April 21 issue of Science Express, "suggests that it’s time to reconsider how we define self versus non-self," Mazmanian says.

Like other commensal gut bacteria—that those that provide nutrients and other benefits to their hosts, without causing harm—B. fragilis was thought to live within the interior of the gut (the lumen), and thus far away from the immune system. "The dogma is that the immune system doesn’t respond to symbiotic bacteria because of immunological ignorance," Mazmanian explains. "If we can’t see them, we won’t react to them."

But using a technique called whole-mount confocal microscopy to study the intestines of mice, he and his colleagues found that the bacteria actually live in a unique ecological niche, deep within the crypts of the colon, "and thus in intimate contact with the gut mucosal immune system," he says.

"The closeness of this association highlights that an active communication is occurring between the bacteria and their host," says Caltech postdoctoral scholar June L. Round.

From that vantage point, the bacteria are able to orchestrate control over the immune system—and, specifically, over the behavior of immune cells known as regulatory T cells, or Treg cells. The normal function of Treg cells is to prevent the immune system from reacting against our own tissues, by shutting down certain immune responses; they therefore prevent autoimmune reactions (which, when uncontrolled, can lead to diseases such as multiple sclerosis, type 1 diabetes, lupus, psoriasis, and Crohn's disease).

Bacteroides fragilis has evolved to produce a molecule that tricks the immune system into activating Treg cells in the gut, but in this case, Mazmanian says, "the purpose is to keep the cells from attacking the bugs. Beautiful, right?"

In their Science paper, Mazmanian and colleagues describe the entire molecular pathway that produces this effect. It starts with the bacteria producing a complex sugar molecule called polysaccharide A (PSA). PSA is sensed by particular receptors, known as Toll-like receptors, on the surfaces of Treg cells, thus activating those cells specifically. In response, Treg cells suppress yet another type of cell, the T helper 17 (Th17) cells. Normally, Th17 cells induce pro-inflammatory responses—those that would result, for example, in the elimination of foreign bacteria or other pathogens from the body. By shutting those cells down, B. fragilis gets a free pass to colonize the gut. "Up until now, we have thought that triggering of Toll-like receptors resulted solely in the induction of pathways that eliminate bacteria," says Round. "However, our studies suggest that multiple yet undiscovered host pathways allow us to coexist with our microbial partners."

When Mazmanian and his colleagues blocked this mechanism—by removing the PSA molecule, by removing the Toll-like receptor for PSA, or by eliminating the Treg cells themselves—the bacteria were...
attacked by the immune system and expelled. "They can no longer co-opt the immune system into inducing an anti-inflammatory response, so the formerly benign bacterium now looks like a pathogen," he says, "although the bug itself is exactly the same."

"Our immune system arose in the face of commensal colonization and thus likely evolved specialized molecules to recognize good bacteria," says Round. Mazmanian suspects that genetic mutations in these pathways could be responsible for certain types of immune disorders, including inflammatory bowel disease: "The question is, do patients get sick because they are rejecting bacteria they shouldn't reject?"

On a more philosophical level, Mazmanian says, the findings suggest that our concept of "self" should be broadened to include our many trillions of microbial residents. "These bacteria live inside us for our entire lives, and they've evolved to look and act like us, as part of us," he says. "As far as our immune system is concerned, the molecules made by gut bacteria should be tolerated similarly to our own molecules. Except in this case, the bacteria 'teaches' us to tolerate them, for both our benefit and theirs."

At-Home STD Tests Private, but Sometimes Wrong

A few for-profit firms are selling at-home STD tests with the promise of saving money, time and possible embarrassment. The Food and Drug Administration (FDA), however, has not approved the companies' kits, and one study found their accuracy was hit-or-miss.

"We wanted to see if people were [processing] these tests on their dining room table or in a barn," said Charlotte Gaydos, an STD and public health expert at the Johns Hopkins University School of Medicine. Last year, she put the testing services of several companies through a test of her own. Of six websites from which kits could be ordered, two never returned results. Of the remainder, half returned false-negative results, though Gaydos ensured the samples contained chlamydia.

FDA issued a warning last November to Identigene, whose unapproved kits were being sold through Rite-Aid stores. Identigene declined to say how many of the $119 kits it has sold; it said it is working to win FDA approval and anticipates being in compliance by late summer.

With CDC's cooperation, Gaydos and her team created a web-based testing service that offers free at-home STD kits through www.IWantTheKit.org or by telephone. With grant funding, the program sends at-home kits free to addresses in Alaska, Denver, Maryland, West Virginia, Philadelphia, District of Columbia, and some Illinois counties. The 2,600 women and 900 men screened so far had two to three times the STD prevalence found among persons who test at family planning clinics, Gaydos said.

Modeled on the Hopkins program, Los Angeles County's www.DontThinkKnow.org website also is a free at-home testing service. Of 1,619 tests returned to the program, 8.5 percent tested positive for chlamydia, 6.8 percent for gonorrhea, and 4.8 percent both. First-year cost was $50,470, "a very good start for something that has not been done before," said county Public Health Director Dr. Jonathan Fielding.

More College 'Hookups,' but More Virgins, Too

Casual sex, or "hooking up," is very common among college students. However, the proportion choosing to remain abstinent through their early twenties has recently grown.

Hooking up is ubiquitous, in part, because women outnumber men on many campuses, said Mark Regnerus, a sociologist at the University of Texas-Austin.

"The women wind up competing with each other for access to the men, and often, that means relationships become sexual quicker," said Regnerus, summarizing an analysis of four national studies involving 25,000 people ages 18-23 and 200 interviews.

"For the majority of students, they're not going to dinner and a movie unless they've hooked up with someone," said Justin Garcia, a Binghamton University doctoral fellow who researches the phenomenon. "Some physical interaction comes before the dating."

The no-strings relationships could reflect the fast-paced academic calendar, including studying abroad, internships, and a graduate school career, said sociologist Teresa Downing-Matibag of Iowa State University. The economic downturn also forced many students to juggle work and school, leaving even less time to develop relationships.

But the pressures of a career-centered approach to college may be leading some students to remain abstinent. Of those ages 20-24 surveyed in a CDC study during 2006-08, 12 percent of women and 13 percent of men reported they remained virgins - up from 8 percent for each in 2002.
“Friends my age have not said they have chosen to remain virgins,” but “a lot of my peers, as women, have got a lot of other things going on,” said Ashley Thompson, 23, a student of public health at Ohio State University-Columbus. “I think the fact that young women are able to focus on other life goals such as school or career could change the way they form relationships, which inherently would impact their sexual activity.”

**Morning-After Pill Linked to STD Rise**

*United Press International*, (02.01.2011)

University of Nottingham researchers reported in a new study that teenagers' STD diagnoses and conception rates rose in areas of England where druggists offered emergency morning-after contraception.

Since 2000, local authorities in England have been encouraged to provide emergency contraception in pharmacies, free of charge and without a prescription, to teens age 16 and younger. Many municipalities have introduced programs, while others declined to do so, explained professors David Paton and Sourafel Girma.

Local data from 1998 to 2004 indicated that areas operating pharmacy-based emergency birth control programs showed an average 5 percent increase in the STD rate among teenagers. For youths 16 and under, the increase was 12 percent. The programs also were associated with a small increase in the number of teen pregnancies, the study found.

In a statement, Paton said the results show “how government interventions can sometimes lead to unfortunate unintended consequences. The fact that [STD] diagnoses increased in areas with emergency birth control schemes will raise questions over whether these schemes represent the best use of public money.”


**House/Ball Culture and Adolescent African-American Transgender Persons and Men Who Have Sex with Men: A Synthesis of the Literature**

*AIDS Care* Vol. 23; No. 4: P. 515-520, (04.2011) Gregory Phillips II; James Peterson; Diane Binson; Julia Hidalgo; Manya Magnus, for the YMSM of Color SPNS Initiative Study Group

Young men of color who have sex with men (YMSM of color) and transgender individuals have been severely impacted by the US HIV/AIDS epidemic. In the United States, “houses” and “balls” have historically been a primary meeting ground for YMSM of color and transgender persons, and thus they offer an opportunity for HIV prevention activities.

“Houses provide a familial structure for YMSM of color and transgender people, while balls provide them with events at which they can congregate for social support and entertainment,” the authors wrote. The team undertook a comprehensive literature search using Scopus and PubMed, Internet sites and HIV prevention and care resources for YMSM of color associated with a multisite evaluation.

While noting that additional studies “are needed to identify culturally appropriate and effective methods of integration of house/ball methods into HIV prevention services aimed at transgender persons and YMSM of color,” the authors’ literature review determined that “houses and balls have been responsive to the HIV/AIDS epidemic.” The networks developed by houses and balls “are critical in providing a social and familiar context for often-disenfranchised youth. The organizations have embraced the need for HIV prevention, and their methodology may be transferable to other prevention contexts,” the authors concluded.

**Genital Herpes Virus Can Spread Despite Lack of Symptoms**

*SUMMARY:* People without genital sores or other symptoms can still shed and transmit herpes simplex virus type 2 (HSV-2) during sex, according to a recent U.S. study.

*By Liz Highleyman*
Herpes simplex virus type 2 is the usual cause of genital herpes, while type 1 typically causes cold sores; both types, however, can infect either area.

HSV causes painful blisters on the skin and mucous membranes and sometimes also flu-like symptoms. Between outbreaks it lies dormant in nerve cells, but can be reactivated by triggered factors such as concurrent infections, hormonal fluctuations, or exposure to sunlight.

As described in the April 13, 2011, *Journal of the American Medical Association*, Anna Wald from the University of Washington and colleagues evaluated the virological and clinical course of genital virus shedding among people with symptomatic and asymptomatic HSV-2 infection.

HSV-2 is among the most common sexually transmitted infections worldwide, with global estimates of 536 million total people infected and 23.6 million new cases each year, Wald explained at a *JAMA* media briefing at the National Press Club in Washington, DC. At any given time many people with HSV-2 will not have lesions or other symptoms, and some individuals rarely or never experience symptoms. A growing number of people are aware they have genital herpes thanks to the availability of commercial HSV-2 antibody tests, but screening is not widespread. In the U.S. an estimated 16% of adults are HSV-2 seropositive, but only 10% to 25% of them have recognized genital herpes. Furthermore, the natural history of HSV-2 infection in asymptomatic seropositive individuals is not fully understood.

The present study included 498 immunocompetent HSV-2 seropositive people enrolled in prospective studies of genital HSV shedding -- an indicator of active viral replication -- at the University of Washington Virology Research Clinic in Seattle and the Westover Heights Clinic in Portland between March 1992 and April 2008. Each participant collected swabs of genital secretions daily for at least 30 days. The researchers then used quantitative real-time polymerase chain reaction (PCR) assays to measure HSV-2 in samples.

**Results**

- HSV-2 was detected on 4753 of 23,683 total days, or 20% of the time, among 410 people with symptomatic genital herpes.
- HSV-2 was detected on 519 of 5070 total days, or about 10% of the time, among 88 individuals with consistently asymptomatic infection.
- Genital HSV-2 was detected at least once in 342 of 410 people (83%) with symptomatic infection and in 60 of 88 people (68%) with asymptomatic infection during an average 57 days of follow-up.
- Subclinical shedding in the absence of symptoms was significantly more common among people with symptomatic HSV-2 infection compared with asymptomatic infection (2708 of 20,735 days or 13% vs 434 of 4929 days or 9%).
- However the amount of HSV-2 detected during subclinical shedding episodes was similar in the symptomatic and asymptomatic groups (median 4.3 vs 4.2 log copies, respectively).
- People with symptomatic infection had more frequent genital HSV-2 shedding episodes than people with asymptomatic infection (median 17.9 vs 12.5 episodes per year).
- Days with evident lesions accounted for 2045 of 4753 days with genital virus shedding (43%) among people with symptomatic genital HSV-2 infection compared with 85 of 519 days (16%) among people with asymptomatic infection.

Based on these findings, the study authors concluded, "Persons with asymptomatic HSV-2 infection shed virus in the genital tract less frequently than persons with symptomatic infection, but much of the difference is attributable to less frequent genital lesions because lesions are accompanied by frequent viral shedding."
Though less common, HSV-2 shedding did occur among asymptomatic people without evident genital lesions, indicating that such individuals may transmit the virus between outbreaks of symptoms.

"Our findings suggest that 'best practices' management of HSV-2-infected persons who learn that they are infected from serologic testing should include anticipatory guidance with regard to genital symptoms, as well as counseling about the potential for transmission," Wald recommended at the press conference.

"The issue of infectivity is both a patient management and a public health concern."

Measures including condom use and daily valacyclovir (Valtrex) treatment can help decrease HSV-2 transmission to sex partners, but risk reduction is not complete and many people do not take advantage of such measures because they do not realize they are infected. It is a common misconception that HSV-2 can only be transmitted when lesions are present, indicating the need for better public health education in this area.

4/23/11

Reference

**GeoVax and HIV Trials Network To Test Prime-Boost Vaccine**

**SUMMARY:** GeoVax Labs this month announced that it will test a novel recombinant HIV prevention vaccine that showed promise in monkeys, in collaboration with NIAID and the HIV Vaccine Trials Network.

Below is an edited excerpt from a recent GeoVax press release describing the vaccine candidate and forthcoming clinical trials.

**Expansion of HIV/AIDS Vaccine Program Announced by GeoVax Labs, Inc.**

**Adjuvant Gives 70% Prevention of Infection in Primates**

Atlanta, GA -- April 11, 2011 -- GeoVax Labs, Inc. (OTCQB/OTCBB: GOVX) announced today that it is expanding its preventative HIV/AIDS vaccine development effort in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), part of the U.S. National Institutes of Health (NIH) and the HIV Vaccine Trials Network (HVTN).

Specifically, the HVTN plans to clinically test a novel vaccine product developed by GeoVax scientists that expresses human granulocyte-macrophage colony stimulating factor (GM-CSF) in combination with inactivated HIV proteins. The novel vaccine consists of a recombinant DNA vaccine co-expressing human GM-CSF and non-infectious HIV virus-like particles. The DNA vaccine is used to prime immune responses that are subsequently boosted by vaccination with a recombinant modified vaccinia Ankara (MVA) vectored vaccine. The MVA expresses the HIV virus-like-particles, but does not express GM-CSF. The regimen builds on the GeoVax DNA/MVA vaccine that is currently in Phase 2a clinical testing through the HVTN.

GM-CSF is a cytokine (growth stimulating protein) that serves to expand and mature cells that initiate immune responses and has undergone extensive testing in humans for cancer vaccines. The GM-CSF-adjuvanted vaccine was added to GeoVax's portfolio because of the outstanding ability of the simian prototype vaccine to induce immune responses that prevented simian immunodeficiency virus (SIV) infection. In nonhuman primates, the GM-CSF-enhanced vaccine achieved protection against SIV in 70% of the animals. Protection was measured against 12 weekly rectal challenges using a dose of SIV which is estimated to be 30 to 300 times higher than the typical exposure dose of HIV in mucosal transmission in humans.

"For years, the HIV vaccine field has been working with vaccines that elicited immune responses that primarily controlled immunodeficiency virus challenges in infected animals, but did not actually prevent infections. The ultimate goal is to prevent infections. The co-expression of GM-CSF with the SIV proteins is a vaccine design that appears to be a large step towards reaching this goal," said Dr. Harriet Robinson, Chief Scientific Officer at GeoVax. "In our trials in nonhuman primates, GM-CSF enhanced the quality of the SIV-specific antibody response. Antibody is present in blood and tissues and has the potential of blocking SIV before it infects cells. The GM-CSF-adjuvanted vaccine induced the production of antibodies characterized with increased tightness of antibody binding. The tightness of antibody binding, known as avidity, can be expressed as an index. Animals with indices above 40 were protected from infection, whereas animals with lower indices were infected with the number of challenges to infection correlating with their index."
"We are very pleased that the HVTN will be conducting trial HVTN 094 of our GM-CSF adjuvanted vaccine product, which we expect will begin late this year," said Dr. Robert McNally, CEO of GeoVax. "The HVTN, funded by the NIAID, is the largest worldwide clinical trials network dedicated to the development and testing of HIV/AIDS vaccines. We are looking forward to working with an excellent team of HVTN trial investigators."

**About GeoVax Labs, Inc.**

GeoVax is a biotechnology company developing human vaccines for diseases caused by HIV (Human Immunodeficiency Virus — that leads to AIDS) and other infectious agents. Our goals include developing HIV/AIDS vaccines for global markets, overseeing the manufacture and testing of these vaccines under GMP/GLP conditions (FDA guidelines), conducting clinical trials for vaccine safety and effectiveness, and obtaining regulatory approvals to move the product forward. GeoVax's vaccines are unique in expressing virus like particles that display the trimeric membrane bound form of the HIV-1 envelope glycoprotein. All preventative Phase 1 human clinical trials conducted to date tested various combinations and doses of our DNA and MVA vaccines, their ability to raise anti-HIV humoral (antibody) and cellular (cytotoxic T-cell) immune responses, as well as, the vaccines' safety. Successful results from Phase 1 testing supported the initiation of the first Phase 2 testing. GeoVax's Phase 2 human trial began in January 2009 and will ultimately involve 300 participants at sites in the United States and South America. Recently GeoVax began enrolling patients in a Phase 1 therapeutic trial for individuals already infected with HIV. For more information, please visit [www.geovax.com](http://www.geovax.com).

**About the HVTN**

The HIV Vaccine Trials Network (HVTN) is the largest worldwide clinical trials network dedicated to the development and testing of HIV/AIDS vaccines. The HVTN is an international collaboration that conducts all phases of clinical trials, from evaluating experimental vaccines for safety and the ability to stimulate immune responses, to testing vaccine efficacy. Support for the HVTN comes from the National Institute of Allergy and Infectious Diseases (NIAID), part of the U.S. National Institutes of Health (NIH). The Network's HIV Vaccine Trial Units are located at leading research institutions in 27 cities on four continents. The Network's headquarters are at the Fred Hutchinson Cancer Research Center in Seattle, Washington. 4/23/11

**New approach to defeating flu shows promise**

New research on mice has shown that pulmonary administration of granulocyte macrophage-colony stimulating factor (GM-CSF) significantly reduces flu symptoms and prevents death after a lethal dose influenza virus. While GM-CSF therapy for humans as a flu prophylaxis or treatment may be years away, the study results were striking: All of the mice treated with GM-CSF survived after being infected with the influenza virus, whereas untreated mice all died from the same infection.

"Such unique and unambiguous results demonstrate the great potential of GM-CSF and may be the remedy for a critical public health priority: developing strategies to reduce the morbidity and mortality from influenza," said Homayoun Shams, PhD, principal investigator of the study.

The results were posted online ahead of the print edition of the *American Journal of Respiratory and Critical Care Medicine*. Each year, flu infects 3 to 5 million people worldwide and is responsible for 250-500,000 deaths, according to the World Health Organization. Genetic mutations of influenza virus reduce the potency of flu vaccines, and a vaccinated person may contract flu, develop complications and even die due to poor host immune responses to vaccine or mutated virus strains.

Vaccinations work by activating the host's adaptive immunity in advance of infection. However, if the immune system is compromised, a vaccination may not provoke an adequate immune response to confer protection. Additionally, vaccine-induced immunity takes time to develop. If an individual is exposed shortly before or after being vaccinated, the vaccine will likely have little or no effect on his or her immunity.

"Improved methods to protect against influenza are sorely needed, particularly in the face of an impending pandemic. Development of such methods hinges on understanding host mechanisms that confer robust protection against influenza," said Dr. Shams. "Despite the widespread use of vaccines, influenza causes significant morbidity and mortality throughout the world, and those with poor immune systems are particularly more susceptible—such as very young, elderly or immunocompromised individuals."
GM-SCF boosts innate immunity to make it immediately effective against the virus, and its protective effect has not been shown to be strain dependant so far. Alveolar macrophages (AM), which are enhanced by GM-SCF, are an essential piece of the innate immune response and are known to contribute to host defense against flu infections in animal models.

"Unlike a vaccine, GM-SCF does not rely heavily on the body's ability to mount an immune counter-attack against a specific antigen or virus strain, but enhances the speed of local responses to virus infection and delicately balances the host immune responses," explained Dr. Shams.

Dr. Shams and colleagues wanted to test the idea that boosting AM by introducing GM-SCF would protect against flu. They used three types of mice to test their hypothesis: wild-type (WT) mice, transgenic mice that do not express any GM-SCF (GM-/−), and transgenic mice that express GM-SCF only in the lung (SPC-GM). They infected all three strains of mice with lethal doses of influenza virus. After progressive weight loss, all WT and GM-/− mice died within days. In contrast, all SPC-GM mice survived, and they gained back the weight they initially lost after a short period.

"This proves the concept that GM-SCF, only in the lung, is sufficient to provide complete protection against infection with otherwise lethal doses of influenza virus strains," said Dr. Shams. "This finding delineates a novel means of conferring marked resistance to influenza through enhancing innate immune mechanisms that depend on AM. We found that SPC-GM mice that overexpress GM-SCF only in the lungs are highly resistant to infection with laboratory and clinical influenza strains, including the recent pandemic swine H1N1 strain."

GM-SCF is already in use in humans as a therapy for neutropenia, and Dr. Shams hopes to eventually test its effectiveness in clinical trials for preventing or treating flu exposure. "If additional work determines that delivery of GM-SCF to the lungs after onset of symptoms improves the outcome of influenza infection, this strategy has great potential to represent a new intervention to reduce morbidity and mortality from influenza in humans," he said.

Nature's Elegant Solution to Repairing DNA in Cancer, Other Conditions
ScienceDaily (Apr. 21, 2011) — A major discovery about an enzyme's structure has opened a window on understanding DNA repair. Scientists at Duke University Medical Center have determined the structure of a nuclease that will help scientists to understand several DNA repair pathways, a welcome development for cancer research.

DNA repair pathways are very important in the context of cancer biology and aging, but the tools the cell uses to do those repairs are not well understood.

"Until we saw the structure using X-ray crystallography, we didn't understand how it could recognize so many unusual DNA structures," said senior author Lorena Beese, Ph.D., James B. Duke Professor of Biochemistry. "The relative arrangement of the binding sites and of the active site itself for this enzyme is important for recognition during the repair process, and I don't think we could have imagined how it came together."

The study appears in this week's issue of Cell journal.

"We present the first structural information about these nucleases in humans, and that information is important for DNA substrate recognition and enzymatic mechanism," Beese said. "The discovery is important for understanding the mismatch repair pathway, and more generally, it will help us understand other pathways as well."

If mismatch repairs are not completed properly, this deficiency can have profound effects on human health, including genes that mutate spontaneously, forms of colorectal cancer, and the development of an estimated 15-25 percent of sporadic tumors, the authors noted.

"Scientists have been interested in obtaining a detailed picture of where the atoms are in this protein for a long time. We were able to determine the structure, because we put together the right experiments at the right time -- good protein expression, good purification, and fortunately when we got crystals we had the right team to solve the structure and do the biochemical experiments," Beese said. "This was truly a team effort."

The next step is to study complexes of this molecule with other proteins in the repair pathway. "By understanding the interactions between proteins, we will get more insight into how it works and how the activities are regulated," Beese said. "In terms of future therapeutic strategies, these interfaces present exciting targets for new drugs."

Also to be published in the April 14 issue of Cell, a team lead by John Tainer at the Lawrence Berkeley labs reports that another nuclease in a related pathway has the same structural arrangements.
"It’s remarkable how nature has solved complex topological puzzles in DNA substrate recognition with such elegant simplicity," Beese said.

**Journal Reference:**

**Salmonella Utilize Multiple Modes of Infection: New Mechanism That Helps With Invading Host Cells Discovered**
ScienceDaily (Apr. 22, 2011) — Scientists from the Helmholtz Centre for Infection Research (HZI) in Braunschweig, Germany have discovered a new, hitherto unknown mechanism of *Salmonella* invasion into gut cells: In this entry mode, the bacteria exploit the muscle power of cells to be pulled into the host cell cytoplasm. Thus, the strategies *Salmonella* use to infect cells are more complex than previously thought.

According to the World Health Organization, the number of *Salmonella* infections is continuously rising, and the severity of infections is increasing. One of the reasons for this may be the sophisticated infection strategies the bacteria have evolved. The striking diversity of invasion strategies may allow *Salmonella* to infect multiple cell types and different hosts.

"*Salmonella* do not infect their hosts according to textbook model," says Theresia Stradal, group leader at the Helmholtz Centre in Braunschweig, who has recently accepted a call to the University of Münster. "Only a single infection mechanism has seriously been discussed in the field up till now – without understanding all the details," adds Klemens Rottner, now Professor at the University of Bonn.

All entry mechanisms employed by *Salmonella* target the so-called actin cytoskeleton of the host cell. Actin can polymerise into fine and dynamic fibrils, also called filaments, which associate into networks or fibres. These structures stabilise the cell and enable it to move, as they are constantly built up and taken down. One of the most important core elements is the Arp2/3 complex that nucleates the assembly of actin monomers into filaments.

Extensions of the cell membrane are filled with actin filaments. In the commonly accepted infection mechanism, *Salmonella* abuses the Arp2/3 complex to enter the host cell: the bacteria activate the complex and thus initiate the formation actin filaments and development of prominent membrane extensions, so-called ruffles. These ruffles surround and enclose the bacteria so that they end up in the cell interior. Last year, the research groups headed by Theresia Stradal and Klemens Rottner discovered that *Salmonella* can also reach the cell interior without initiating membrane ruffles. With this, the researchers disproved a long-standing dogma.

their recent study, the experts from Braunschweig now describe a completely unknown infection mechanism. The results have just appeared in the latest issue of the journal *Cell Host & Microbe*. In this new infection mechanism, *Salmonella* also manipulate the actin cytoskeleton of the host cell. This time, however, they do not induce the generation of new filaments, but activate the motor protein myosin II. The interplay of actin and myosin II in muscle cells is well known: in a contracting muscle, myosin and actin filaments slide along each other and this way shorten the muscle; it contracts.

In epithelial cells, the contractile structures are less organised but work similarly. Here, actin and myosin II form so-called stress fibres that tightly connect to the membrane. During an infection, stress fibres at the entry site can contract and pull the bacteria into the cell. "This way of infection operates independently from the Arp2/3 complex, the central component of the 'classic' infection mechanism," says Jan Hänisch, who worked on this project as postdoctoral researcher.

**Journal Reference:**

**Anti-HIV Vaginal Gel Promising for Protection in Africa, SE Asia**
ScienceDaily (Apr. 22, 2011) — A new vaginal microbicide gel and drug formulation looks promising for empowering women in developing countries to protect themselves from HIV during intercourse, without having to inform their partners, according to research published in the April 2011 issue of the journal *Antimicrobial Agents and Chemotherapy*.

HIV infection remains a major risk for women in sub-Saharan Africa and Southeast Asia, and one over which women often have little control due to unequal gender status over much of those regions. Investigators say the gel, the subject of the current research, will be cost-effective for such women, and
laboratory studies suggest the gel-drug combination will be safe and effective. ImQuest BioSciences, Inc., the drug’s developer, hopes to have the gel-drug combination in human clinical trials in 2012.

One of the drug’s most important attributes is that it has two distinct mechanisms of action. IQP-0528, as the drug is known, inhibits the virus' ability to enter human cells, as well as the reverse transcription of the virus' genome into the host genome, "which is required for productive infection of the cell," says Robert Buckheit, of ImQuest BioSciences, of Frederick, MD. In that sense, IQP-0528 is like two drugs in one. Laboratory studies suggest that the product will work very effectively.

The investigators assayed a number of candidate drugs before choosing IQP-0528. Some of the other drugs were chemically unstable, or unstable at pH values to which they would be exposed, or otherwise unstable, says corresponding author Patrick F. Kiser of the University of Utah, Salt Lake City. It was critical for the formulation to be stable at ambient temperatures of sub-Saharan Africa, as refrigeration is not widely available in much of that region.

ImQuest continues to investigate a variety of options for drug, gel, and device formulations. "At present we have gels, intravaginal ring, and biofilm formulations of IQP-0528, in addition to the gel described in the paper, and products developed, which include combinations of IQP-0528 with tenofovir, which was recently found to inhibit the sexual transmission of HIV," says Buckheit. All this is in the interest of developing a product which women can use most easily and comfortably.

Kiser is particularly proud of the "symphony of tools and techniques used in the study. We had virology, human explant studies, chemical and physical stability studies, transport studies, and permeability studies of the drug," he says. "Putting all those things together is not trivial."

Journal Reference:

Bacteria Interrupted: Disabling Coordinated Behavior and Virulence Gene Expression

ScienceDaily (Apr. 22, 2011) — New research reveals a strategy for disrupting the ability of bacteria to communicate and coordinate the expression of virulence factors. The study, published in the April 22nd issue of the journal Molecular Cell, may lead to the development of new antibacterial therapeutics.

Bacteria use a process called "quorum sensing" to synchronize group behaviors that promote pathogenesis. During the process of quorum sensing, bacteria communicate with one another via chemical signals called autoinducers. As the population increases, so do autoinducer concentrations. Interactions between autoinducers and their receptors control gene expression and underlie coordinated behavior within cell populations.

"Quorum sensing controls virulence factor expression in many clinically relevant pathogens, so quorum sensing antagonists that prevent virulence gene activation offer a potential route to novel antibacterial therapeutics," explains senior study author, Dr. Frederick M. Hughson, from Princeton University. "A handful of quorum sensing antagonists have in fact been discovered, but how they work has remained mysterious." Dr. Hughson's Princeton colleague and co-author of this report, Dr. Bonnie L. Bassler, had previously demonstrated that antagonizing quorum sensing could provide protection from quorum-sensing-mediated killing by the pathogenic bacteria Chromobacterium violaceum. However, before the full therapeutic potential of this approach can be realized, it is necessary to gain a better understanding of exactly how the antagonists disrupt quorum sensing.

Many pathogenic bacteria, including Chromobacterium violaceum, use LuxR family DNA-binding proteins as quorum sensing receptors. In the absence of an autoinducer, LuxR proteins are unstable. However, when an autoinducer binds to LuxR it forms a stable complex that activates virulence genes. Using a battery of methods ranging from genetics to X-ray crystallography, the researchers discovered that the LuxR type protein CviR was potently antagonized by compounds that bound in place of the endogenous autoinducer. The antagonists, unlike the autoinducer, caused CviR to adopt an inactive "closed" conformation that was incapable of binding DNA.

The findings provide insight into the mechanisms that underlie successful antagonism of quorum sensing and may direct development of new antibacterial therapeutics aimed at interfering with bacterial communication. "We demonstrated one successful strategy for inactivating quorum sensing receptors using small drug-like molecules. Small molecules that function analogously to the antagonists we studied could be broadly useful for inhibiting other LuxR-type receptors," concludes Dr. Hughson. "Indeed, this..."
strategy should be readily generalizable to other multi-domain proteins but has not, to our knowledge, previously been demonstrated."

Journal Reference:

Right-Handedness Prevailed 500,000 Years Ago
ScienceDaily (Apr. 20, 2011) — Right-handedness is a distinctively human characteristic, with right-handers outnumbering lefties nine-to-one. But how far back does right-handedness reach in the human story? Researchers have tried to determine the answer by looking at ancient tools, prehistoric art and human bones, but the results have not been definitive.

Now, David Frayer, professor of anthropology at the University of Kansas, has used markings on fossilized front teeth to show that right-handedness goes back more than 500,000 years. He is the lead author (with colleagues in Croatia, Italy and Spain) of a paper published this month in the British journal Laterality.

His research shows that distinctive markings on fossilized teeth correlate to the right or left-handedness of individual prehistoric humans.

"The patterns seen on the fossil teeth are directly and consistently produced by right or left hand manipulation in experimental work," Frayer said.

The oldest teeth come from a more than 500,000-year-old chamber known as Sima de los Huesos near Burgos, Spain, containing the remains of humans believed to be ancestors of European Neandertals. Other teeth studied by Frayer come from later Neandertal populations in Europe.

"These marks were produced when a stone tool was accidentally dragged across the labial face in an activity performed at the front of the mouth," said Frayer. "The heavy scoring on some of the teeth indicates the marks were produced over the lifetime of the individual and are not the result of a single cutting episode."

Overall, Frayer and his co-authors found right-handedness in 93.1 percent of individuals sampled from the Sima de los Huesos and European Neandertal sites.

"It is difficult to interpret these fossil data in any way other than that laterality was established early in European fossil record and continued through the Neandertals," said Frayer. "This establishes that handedness is found in more than just recent Homo sapiens."

Frayer said that his findings on right-handedness have implications for understanding the language capacity of ancient populations, because language is primarily located on the left side of the brain, which controls the right side of the body, there is a right handedness-language connection.

"The general correlation between handedness and brain laterality shows that human brains were lateralized in a 'modern' way by at least half a million years ago and the pattern has not changed since then," he said. "There is no reason to suspect this pattern does not extend deeper into the past and that language has ancient, not recent, roots."

Journal Reference:

Why Most Published Research Findings Are False **** (long)
John P. A. Ioannidis

Summary
There is increasing concern that most current published research findings are false. The probability that a research claim is true may depend on study power and bias, the number of other studies on the same question, and, importantly, the ratio of true to no relationships among the relationships probed in each scientific field. In this framework, a research finding is less likely to be true when the studies conducted in a field are smaller; when effect sizes are smaller; when there is a greater number and lesser preselection of tested relationships; where there is greater flexibility in designs, definitions, outcomes, and analytical modes; when there is greater financial and other interest and prejudice; and when more teams are involved in a scientific field in chase of statistical significance. Simulations show that for most study designs and settings, it is more likely for a research claim to be false than true. Moreover, for many current scientific fields, claimed research findings may often be simply accurate measures of the
prevailing bias. In this essay, I discuss the implications of these problems for the conduct and interpretation of research.

Published research findings are sometimes refuted by subsequent evidence, with ensuing confusion and disappointment. Refutation and controversy is seen across the range of research designs, from clinical trials and traditional epidemiological studies [1–3] to the most modern molecular research [4,5]. There is increasing concern that in modern research, false findings may be the majority or even the vast majority of published research claims [6–8]. However, this should not be surprising. It can be proven that most claimed research findings are false. Here I will examine the key factors that influence this problem and some corollaries thereof.

**Modeling the Framework for False Positive Findings**

Several methodologists have pointed out [9–11] that the high rate of nonreplication (lack of confirmation) of research discoveries is a consequence of the convenient, yet ill-founded strategy of claiming conclusive research findings solely on the basis of a single study assessed by formal statistical significance, typically for a p-value less than 0.05. Research is not most appropriately represented and summarized by p-values, but, unfortunately, there is a widespread notion that medical research articles should be interpreted based only on p-values. Research findings are defined here as any relationship reaching formal statistical significance, e.g., effective interventions, informative predictors, risk factors, or associations. “Negative” research is also very useful. “Negative” is actually a misnomer, and the misinterpretation is widespread. However, here we will target relationships that investigators claim exist, rather than null findings.

As has been shown previously, the probability that a research finding is indeed true depends on the prior probability of it being true (before doing the study), the statistical power of the study, and the level of statistical significance [10,11]. Consider a 2 × 2 table in which research findings are compared against the gold standard of true relationships in a scientific field. In a research field both true and false hypotheses can be made about the presence of relationships. Let R be the ratio of the number of “true relationships” to “no relationships” among those tested in the field. R is characteristic of the field and can vary a lot depending on whether the field targets highly likely relationships or searches for only one or a few true relationships among thousands and millions of hypotheses that may be postulated. Let us also consider, for computational simplicity, circumscribed fields where either there is only one true relationship (among many that can be hypothesized) or the power is similar to find any of the several existing true relationships. The pre-study probability of a relationship being true is \( R / (R + 1) \). The probability of a study finding a true relationship reflects the power \( 1 - \beta \) (one minus the Type II error rate). The probability of claiming a relationship when none truly exists reflects the Type I error rate, \( \alpha \).

Assuming that \( c \) relationships are being probed in the field, the expected values of the 2 × 2 table are given in Table 1. After a research finding has been claimed based on achieving formal statistical significance, the post-study probability that it is true is the positive predictive value, PPV. The PPV is also the complementary probability of what Wacholder et al. have called the false positive report probability [10]. According to the 2 × 2 table, one gets PPV = \( (1 - \beta)R / (R - \beta R + \alpha) \). A research finding is thus more likely true than false if \( (1 - \beta)R > \alpha \). Since usually the vast majority of investigators depend on \( \alpha = 0.05 \), this means that a research finding is more likely true than false if \( (1 - \beta)R > 0.05 \).

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Table 1. Research Findings and True Relationships, doi:10.1371/journal.pmed.0020124.t001

What is less well appreciated is that bias and the extent of repeated independent testing by different teams of investigators around the globe may further distort this picture and may lead to even smaller probabilities of the research findings being indeed true. We will try to model these two factors in the context of similar 2 × 2 tables.
**Bias**

First, let us define bias as the combination of various design, data, analysis, and presentation factors that tend to produce research findings when they should not be produced. Let $u$ be the proportion of probed analyses that would not have been “research findings,” but nevertheless end up presented and reported as such, because of bias. Bias should not be confused with chance variability that causes some findings to be false by chance even though the study design, data, analysis, and presentation are perfect. Bias can entail manipulation in the analysis or reporting of findings. Selective or distorted reporting is a typical form of such bias. We may assume that $u$ does not depend on whether a true relationship exists or not. This is not an unreasonable assumption, since typically it is impossible to know which relationships are indeed true. In the presence of bias (Table 2), one gets $PPV = \frac{1 - \beta}{R + u \beta R + u - u \alpha + u \beta R}$, and $PPV$ decreases with increasing $u$, unless $1 - \beta \leq \alpha$, i.e., $1 - \beta \leq 0.05$ for most situations. Thus, with increasing bias, the chances that a research finding is true diminish considerably. This is shown for different levels of power and for different pre-study odds in Figure 1. Conversely, true research findings may occasionally be annulled because of reverse bias. For example, with large measurement errors relationships are lost in noise [12], or investigators use data inefficiently or fail to notice statistically significant relationships, or there may be conflicts of interest that tend to “bury” significant findings [13]. There is no good large-scale empirical evidence on how frequently such reverse bias may occur across diverse research fields. However, it is probably fair to say that reverse bias is not as common. Moreover measurement errors and inefficient use of data are probably becoming less frequent problems, since measurement error has decreased with technological advances in the molecular era and investigators are becoming increasingly sophisticated about their data. Regardless, reverse bias may be modeled in the same way as bias above. Also reverse bias should not be confused with chance variability that may lead to missing a true relationship because of chance.
Testing by Several Independent Teams

Several independent teams may be addressing the same sets of research questions. As research efforts are globalized, it is practically the rule that several research teams, often dozens of them, may probe the same or similar questions. Unfortunately, in some areas, the prevailing mentality until now has been to focus on isolated discoveries by single teams and interpret research experiments in isolation. An increasing number of questions have at least one study claiming a research finding, and this receives unilateral attention. The probability that at least one study, among several done on the same question, claims a statistically significant research finding is easy to estimate. For \( n \) independent studies of equal power, the \( 2 \times 2 \) table is shown in Table 3: 

\[
\text{PPV} = \frac{R(1 - \beta^n)}{R + 1 - (1 - \alpha)^n - R\beta^n} \quad (n \text{ not considering bias})
\]

With increasing number of independent studies, PPV tends to decrease, unless \( 1 - \beta < a \), i.e., typically \( 1 - \beta < 0.05 \). This is shown for different levels of power and for different pre-study odds in Figure 2. For \( n \) studies of different power, the term \( \beta^n \) is replaced by the product of the terms \( \beta_i \) for \( i = 1 \) to \( n \), but inferences are similar.

Figure 1. PPV (Probability That a Research Finding Is True) as a Function of the Pre-Study Odds for Various Levels of Bias, \( u \). Panels correspond to power of 0.20, 0.50, and 0.80. 

doi:10.1371/journal.pmed.0020124.g001
Figure 2. PPV (Probability That a Research Finding Is True) as a Function of the Pre-Study Odds for Various Numbers of Conducted Studies, n
Corollaries Top

A practical example is shown in Box 1. Based on the above considerations, one may deduce several interesting corollaries about the probability that a research finding is indeed true.

**Box 1. An Example: Science at Low Pre-Study Odds**

Let us assume that a team of investigators performs a whole genome association study to test whether any of 100,000 gene polymorphisms are associated with susceptibility to schizophrenia. Based on what we know about the extent of heritability of the disease, it is reasonable to expect that probably around ten gene polymorphisms among those tested would be truly associated with schizophrenia, with relatively similar odds ratios around 1.3 for the ten or so polymorphisms and with a fairly similar power to identify any of them. Then $R = 10/100,000 = 10^{-4}$, and the pre-study probability for any polymorphism to be associated with schizophrenia is also $R/(R + 1)$ = $10^{-4}$. Let us also suppose that the study has 60% power to find an association with an odds ratio of 1.3 at $\alpha = 0.05$. Then it can be estimated that if a statistically significant association is found with the $p$-value barely crossing the 0.05 threshold, the post-study probability that this is true increases about 12-fold compared with the pre-study probability, but it is still only $12 \times 10^{-4}$.

Now let us suppose that the investigators manipulate their design, analyses, and reporting so as to make more relationships cross the $p = 0.05$ threshold even though this would not have been crossed with a perfectly adhered to design and analysis and with perfect comprehensive reporting of the results, strictly according to the original study plan. Such manipulation could be done, for example, with serendipitous inclusion or exclusion of certain patients or controls, post hoc subgroup analyses, investigation of genetic contrasts that were not originally specified, changes in the disease or control definitions, and various combinations of selective or distorted reporting of the results. Commercially available “data mining” packages actually are proud of their ability to yield statistically significant results through data dredging. In the presence of bias with $u = 0.10$, the post-study probability that a research finding is true is only $4.4 \times 10^{-4}$. Furthermore, even in the absence of any bias, when ten independent research teams perform similar experiments around the world, if one of them finds a formally statistically significant association, the probability that the research finding is true is only $1.5 \times 10^{-4}$, hardly any higher than the probability we had before any of this extensive research was undertaken!

**Corollary 1: The smaller the studies conducted in a scientific field, the less likely the research findings are to be true.** Small sample size means smaller power and, for all functions above, the PPV for a true research finding decreases as power decreases towards $1 - \beta = 0.05$. Thus, other factors being equal, research findings are more likely true in scientific fields that undertake large studies, such as randomized controlled trials in cardiology (several thousand subjects randomized) [14] than in scientific fields with small studies, such as most research of molecular predictors (sample sizes 100-fold smaller) [15].

**Corollary 2: The smaller the effect sizes in a scientific field, the less likely the research findings are to be true.** Power is also related to the effect size. Thus research findings are more likely true in scientific fields with large effects, such as the impact of smoking on cancer or cardiovascular disease (relative risks 3–20), than in scientific fields where postulated effects are small, such as genetic risk factors for multigenetic diseases (relative risks 1.1–1.5) [7]. Modern epidemiology is increasingly obliged to target smaller effect sizes [16]. Consequently, the proportion of true research findings is expected to decrease. In the same line of thinking, if the true effect sizes are very small in a scientific field, this field is likely to be plagued by almost ubiquitous false positive claims. For example, if the majority of true genetic or nutritional determinants of complex diseases confer relative risks less than 1.05, genetic or nutritional epidemiology would be largely utopian endeavors.
Corollary 3: The greater the number and the lesser the selection of tested relationships in a scientific field, the less likely the research findings are to be true. As shown above, the post-study probability that a finding is true (PPV) depends a lot on the pre-study odds (R). Thus, research findings are more likely true in confirmatory designs, such as large phase III randomized controlled trials, or meta-analyses thereof, than in hypothesis-generating experiments. Fields considered highly informative and creative given the wealth of the assembled and tested information, such as microarrays and other high-throughput discovery-oriented research [4,8,17], should have extremely low PPV.

Corollary 4: The greater the flexibility in designs, definitions, outcomes, and analytical modes in a scientific field, the less likely the research findings are to be true. Flexibility increases the potential for transforming what would be “negative” results into “positive” results, i.e., bias, u. For several research designs, e.g., randomized controlled trials [18–20] or meta-analyses [21,22], there have been efforts to standardize their conduct and reporting. Adherence to common standards is likely to increase the proportion of true findings. The same applies to outcomes. True findings may be more common when outcomes are unequivocal and universally agreed (e.g., death) rather than when multifarious outcomes are devised (e.g., scales for schizophrenia outcomes) [23]. Similarly, fields that use commonly agreed, stereotyped analytical methods (e.g., Kaplan-Meier plots and the log-rank test) [24] may yield a larger proportion of true findings than fields where analytical methods are still under experimentation (e.g., artificial intelligence methods) and only “best” results are reported. Regardless, even in the most stringent research designs, bias seems to be a major problem. For example, there is strong evidence that selective outcome reporting, with manipulation of the outcomes and analyses reported, is a common problem even for randomized trails [25]. Simply abolishing selective publication would not make this problem go away.

Corollary 5: The greater the financial and other interests and prejudices in a scientific field, the less likely the research findings are to be true. Conflicts of interest and prejudice may increase bias, u. Conflicts of interest are very common in biomedical research [26], and typically they are inadequately and sparsely reported [26,27]. Prejudice may not necessarily have financial roots. Scientists in a given field may be prejudiced purely because of their belief in a scientific theory or commitment to their own findings. Many otherwise seemingly independent, university-based studies may be conducted for no other reason than to give physicians and researchers qualifications for promotion or tenure. Such nonfinancial conflicts may also lead to distorted reported results and interpretations. Prestigious investigators may suppress via the peer review process the appearance and dissemination of findings that refute their findings, thus condemning their field to perpetuate false dogma. Empirical evidence on expert opinion shows that it is extremely unreliable [28].

Corollary 6: The hotter a scientific field (with more scientific teams involved), the less likely the research findings are to be true. This seemingly paradoxical corollary follows because, as stated above, the PPV of isolated findings decreases when many teams of investigators are involved in the same field. This may explain why we occasionally see major excitement followed rapidly by severe disappointments in fields that draw wide attention. With many teams working on the same field and with massive experimental data being produced, timing is of the essence in beating competition. Thus, each team may prioritize on pursuing and disseminating its most impressive “positive” results. “Negative” results may become attractive for dissemination only if some other team has found a “positive” association on the same question. In that case, it may be attractive to refute a claim made in some prestigious journal. The term Proteus phenomenon has been coined to describe this phenomenon of rapidly alternating extreme research claims and extremely opposite refutations [29]. Empirical evidence suggests that this sequence of extreme opposites is very common in molecular genetics [29].

These corollaries consider each factor separately, but these factors often influence each other. For example, investigators working in fields where true effect sizes are perceived to be small may be more likely to perform large studies than investigators working in fields where true effect sizes are perceived to be large. Or prejudice may prevail in a hot scientific field, further undermining the predictive value of its research findings. Highly prejudiced stakeholders may even create a barrier that aborts efforts at obtaining and disseminating opposing results. Conversely, the fact that a field is hot or has strong invested interests may sometimes promote larger studies and improved standards of research, enhancing the predictive value of its research findings. Or massive discovery-oriented testing may result in such a large yield of significant relationships that investigators have enough to report and search further and thus refrain from data dredging and manipulation.

Most Research Findings Are False for Most Research Designs and for Most Fields Top
In the described framework, a PPV exceeding 50% is quite difficult to get. Table 4 provides the results of simulations using the formulas developed for the influence of power, ratio of true to non-true relationships, and bias, for various types of situations that may be characteristic of specific study designs and settings. A finding from a well-conducted, adequately powered randomized controlled trial starting with a 50% pre-study chance that the intervention is effective is eventually true about 85% of the time. A fairly similar performance is expected of a confirmatory meta-analysis of good-quality randomized trials: potential bias probably increases, but power and pre-test chances are higher compared to a single randomized trial. Conversely, a meta-analytic finding from inconclusive studies where pooling is used to “correct” the low power of single studies, is probably false if $R \leq 1:3$. Research findings from underpowered, early-phase clinical trials would be true about one in four times, or even less frequently if bias is present. Epidemiological studies of an exploratory nature perform even worse, especially when underpowered, but even well-powered epidemiological studies may have only a one in five chance being true, if $R = 1:10$. Finally, in discovery-oriented research with massive testing, where tested relationships exceed true ones 1,000-fold (e.g., 30,000 genes tested, of which 30 may be the true culprits) [30,31], PPV for each claimed relationship is extremely low, even with considerable standardization of laboratory and statistical methods, outcomes, and reporting thereof to minimize bias.

<table>
<thead>
<tr>
<th>$1 - \beta$</th>
<th>$R$</th>
<th>$u$</th>
<th>Practical Example</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.80</td>
<td>1:1</td>
<td>0.10</td>
<td>Adequately powered RCT with little bias and 1:1 pre-study odds</td>
<td>0.85</td>
</tr>
<tr>
<td>0.95</td>
<td>2:1</td>
<td>0.30</td>
<td>Confirmatory meta-analysis of good-quality RCTs</td>
<td>0.85</td>
</tr>
<tr>
<td>0.80</td>
<td>1:3</td>
<td>0.40</td>
<td>Meta-analysis of small inconclusive studies</td>
<td>0.41</td>
</tr>
<tr>
<td>0.20</td>
<td>1:5</td>
<td>0.20</td>
<td>Underpowered, but well-performed phase I/II RCT</td>
<td>0.23</td>
</tr>
<tr>
<td>0.20</td>
<td>1:5</td>
<td>0.80</td>
<td>Underpowered, poorly performed phase I/II RCT</td>
<td>0.17</td>
</tr>
<tr>
<td>0.80</td>
<td>1:10</td>
<td>0.30</td>
<td>Adequately powered exploratory epidemiological study</td>
<td>0.20</td>
</tr>
<tr>
<td>0.20</td>
<td>1:10</td>
<td>0.30</td>
<td>Underpowered exploratory epidemiological study</td>
<td>0.12</td>
</tr>
<tr>
<td>0.20</td>
<td>1:1,000</td>
<td>0.80</td>
<td>Discovery-oriented exploratory research with massive testing</td>
<td>0.0010</td>
</tr>
<tr>
<td>0.20</td>
<td>1:1,000</td>
<td>0.20</td>
<td>As in previous example, but with more limited bias (more standardized)</td>
<td>0.0015</td>
</tr>
</tbody>
</table>

Table 4. PPV of Research Findings for Various Combinations of Power ($1 - \beta$), Ratio of True to Not-True Relationships ($R$), and Bias ($u$)

Claimed Research Findings May Often Be Simply Accurate Measures of the Prevailing Bias

As shown, the majority of modern biomedical research is operating in areas with very low pre- and post-study probability for true findings. Let us suppose that in a research field there are no true findings at all to be discovered. History of science teaches us that scientific endeavor has often in the past wasted effort in fields with absolutely no yield of true scientific information, at least based on our current understanding. In such a “null field,” one would ideally expect all observed effect sizes to vary by chance around the null in the absence of bias. The extent that observed findings deviate from what is expected by chance alone would be simply a pure measure of the prevailing bias.

For example, let us suppose that no nutrients or dietary patterns are actually important determinants for the risk of developing a specific tumor. Let us also suppose that the scientific literature has examined
60 nutrients and claims all of them to be related to the risk of developing this tumor with relative risks in the range of 1.2 to 1.4 for the comparison of the upper to lower intake tertiles. Then the claimed effect sizes are simply measuring nothing else but the net bias that has been involved in the generation of this scientific literature. Claimed effect sizes are in fact the most accurate estimates of the net bias. It even follows that between “null fields,” the fields that claim stronger effects (often with accompanying claims of medical or public health importance) are simply those that have sustained the worst biases.

For fields with very low PPV, the few true relationships would not distort this overall picture much. Even if a few relationships are true, the shape of the distribution of the observed effects would still yield a clear measure of the biases involved in the field. This concept totally reverses the way we view scientific results. Traditionally, investigators have viewed large and highly significant effects with excitement, as signs of important discoveries. Too large and too highly significant effects may actually be more likely to be signs of large bias in most fields of modern research. They should lead investigators to careful critical thinking about what might have gone wrong with their data, analyses, and results.

Of course, investigators working in any field are likely to resist accepting that the whole field in which they have spent their careers is a “null field.” However, other lines of evidence, or advances in technology and experimentation, may lead eventually to the dismantling of a scientific field. Obtaining measures of the net bias in one field may also be useful for obtaining insight into what might be the range of bias operating in other fields where similar analytical methods, technologies, and conflicts may be operating.

**How Can We Improve the Situation?**

Is it unavoidable that most research findings are false, or can we improve the situation? A major problem is that it is impossible to know with 100% certainty what the truth is in any research question. In this regard, the pure “gold” standard is unattainable. However, there are several approaches to improve the post-study probability.

Better powered evidence, e.g., large studies or low-bias meta-analyses, may help, as it comes closer to the unknown “gold” standard. However, large studies may still have biases and these should be acknowledged and avoided. Moreover, large-scale evidence is impossible to obtain for all of the millions and trillions of research questions posed in current research. Large-scale evidence should be targeted for research questions where the pre-study probability is already considerably high, so that a significant research finding will lead to a post-test probability that would be considered quite definitive. Large-scale evidence is also particularly indicated when it can test major concepts rather than narrow, specific questions. A negative finding can then refute not only a specific proposed claim, but a whole field or considerable portion thereof. Selecting the performance of large-scale studies based on narrow-minded criteria, such as the marketing promotion of a specific drug, is largely wasted research. Moreover, one should be cautious that extremely large studies may be more likely to find a formally statistical significant difference for a trivial effect that is not really meaningfully different from the null [32–34].

Second, most research questions are addressed by many teams, and it is misleading to emphasize the statistically significant findings of any single team. What matters is the totality of the evidence. Diminishing bias through enhanced research standards and curtailing of prejudices may also help. However, this may require a change in scientific mentality that might be difficult to achieve. In some research designs, efforts may also be more successful with upfront registration of studies, e.g., randomized trials [35]. Registration would pose a challenge for hypothesis-generating research. Some kind of registration or networking of data collections or investigators within fields may be more feasible than registration of each and every hypothesis-generating experiment. Regardless, even if we do not see a great deal of progress with registration of studies in other fields, the principles of developing and adhering to a protocol could be more widely borrowed from randomized controlled trials.

Finally, instead of chasing statistical significance, we should improve our understanding of the range of $R$ values—the pre-study odds—where research efforts operate [10]. Before running an experiment, investigators should consider what they believe the chances are that they are testing a true rather than a non-true relationship. Speculated high $R$ values may sometimes then be ascertained. As described above, whenever ethically acceptable, large studies with minimal bias should be performed on research findings that are considered relatively established, to see how often they are indeed confirmed. I suspect several established “classics” will fail the test [36].

Nevertheless, most new discoveries will continue to stem from hypothesis-generating research with low or very low pre-study odds. We should then acknowledge that statistical significance testing in the report of a single study gives only a partial picture, without knowing how much testing has been done outside the report and in the relevant field at large. Despite a large statistical literature for multiple testing corrections [37], usually it is impossible to decipher how much data dredging by the reporting authors or
other research teams has preceded a reported research finding. Even if determining this were feasible, this would not inform us about the pre-study odds. Thus, it is unavoidable that one should make approximate assumptions on how many relationships are expected to be true among those probed across the relevant research fields and research designs. The wider field may yield some guidance for estimating this probability for the isolated research project. Experiences from biases detected in other neighboring fields would also be useful to draw upon. Even though these assumptions would be considerably subjective, they would be very useful in interpreting research claims and putting them in context.

References Top
recipients in a larger sample in Africa spanning close to 10 years. Rather than people becoming antiretroviral (ART) medication. This finding in couples was consistent with those that Venkatesh, Lurie The factor that did seem to be associated with decreased sexual risk Couples counseling whether a partner's status was known. In all, about 40 percent of the people surveyed knew their partner was also HIV positive. The same proportion didn’t know their partner’s status and 20 percent knew their partners to be HIV-negative. When they know their partner is HIV positive, HIV-negative, or their status was unknown. The risk of the virus spreading within couples is therefore important to address, researchers argue.

PROVIDENCE, R.I. [Brown University] — A new study of sexual risk behaviors within long-term couples in South Africa finds that HIV-positive people take almost as much risk in their sexual behavior when they know their partner is HIV-negative or don’t know their status, as when they know their partner is already infected. At the same time, HIV-positive partners who are on antiretroviral therapy and in intensive counseling do engage in less risky behavior. The Brown University researchers who led the study say both findings suggest that more couples-based HIV counseling is needed in South Africa where about 18 percent of adults carry the virus.

“The concept of Positive Prevention — the idea that one focus of prevention should be among people already infected with HIV since they are the only ones who could infect others — was first floated by the CDC in 2003 but hasn’t really taken hold in sub-Saharan Africa,” said Mark Lurie, professor of community health and a senior author of the study published in advance online April 8 in AIDS Behavior. “This paper clearly points to the urgent need to intervene among people already infected with HIV and especially those in ‘discordant’ relationships — relationships in which their partner is not infected.”

The study surveyed 1,163 sexually active HIV-positive men and women in a primary care program at Chris Hani Baragwanath Hospital in Soweto, near Johannesburg. Researchers led by Brown medical student and Ph.D. candidate Kartik Venkatesh asked whether they knew their closest sexual partner’s HIV status, how often they have sex, how often it is unprotected, and how often they have sex outside that relationship.

Risky couples
Although in some places around the world, specific high-risk groups of HIV-positive people have restricted their riskier sexual activities to people also already infected (a practice called “sero-sorting”), Venkatesh’s survey found that heterosexual couples did not seem to operate that way in South Africa. For example, among HIV-positive people who said their closest partner’s status was either HIV-positive or unknown, 18 percent had unprotected sex with them in the last six months, compared to only 14 percent who knew their partner was already infected.

Risks such as having frequent sex (two sex acts in the last two weeks) and going to a partner outside the primary relationship were somewhat lower with HIV-negative or unknown partners than with HIV-positive partners, but not much more so.

“The difference for partners who were negative or status unknown versus those who were positive was not markedly different,” Venkatesh said.

In all, about 40 percent of the people surveyed knew their partner was also HIV positive. The same proportion didn’t know their partner’s status and 20 percent knew their partners to be HIV-negative. There was no correlation between how long the couples were together (a median of 3.4 years) and whether a partner’s status was known.

Couples counseling
The factor that did seem to be associated with decreased sexual risk-taking behavior was receiving antiretroviral (ART) medication. This finding in couples was consistent with those that Venkatesh, Lurie and others reported last year in the journal AIDS, where they saw less risky behavior among ART recipients in a larger sample in Africa spanning close to 10 years. Rather than people becoming
emboldened by medication and improved health to take more risks — a practice called behavioral disinhibition - people in several African countries have tended to become more careful with treatment. "Why we're seeing this might be due to the fact that treatment is also accompanied by condoms and other prevention messages, so that when individuals are coming to get their treatment they are also getting sexual risk behavior prevention counseling," Venkatesh said. 

Taken together, Venkatesh said, the prevalence of risk in South African couples and the likely role that counseling plays in curbing risk could add up to a significant potential benefit to increasing couples counseling about HIV. By bringing men and women into counseling together, such programs may help overcome power imbalances between men and women that exacerbate the lack of communication about HIV status in some relationships. "HIV prevention and treatment programs need to be more couples-friendly or family-focused," Venkatesh said.

'Going Off the Grid' Helps Some Bacteria Hide from Antibiotics
April 25, 2011
By: Ryan Garcia

COLLEGE STATION, Texas, April 25, 2011 - Call them the Jason Bournes of the bacteria world. Going "off the grid," like rogue secret agents, some bacteria avoid antibiotic treatments by essentially shutting down and hiding until it's safe to come out again, says Thomas Wood, professor in the Artie McFerrin Department of Chemical Engineering at Texas A&M University.

This surreptitious and elaborate survival mechanism is explained in the online April edition of "Nature Chemical Biology," which details the research of Wood and his post doctoral student Xiaoxue Wang along with colleagues Breann Brown, Wolfgang Peti and Rebecca Page of Brown University. "Through our research, we're understanding that some bacteria go to 'sleep,' and that antibiotics only work on bacteria that are metabolically active," Wood explains. "You need actively growing bacteria to be susceptible to antibiotics. If the bacterium goes to sleep, the antibiotics, no matter what they do, are not effective because the bacterium is no longer doing the thing that the antibiotic is trying to shut down."

It's an alternative method for survival, Wood says, that starkly contrasts the widely studied genetically based approaches utilized by bacteria through which bacteria gain resistance to antibiotics as the result of mutations experienced throughout time. This mutation-free response, however, demonstrates that some bacteria need not mutate to survive external stressors, Wood says.

Instead, when triggered by an external stressor such as an antibiotic, a bacterial cell can render itself dormant by triggering an internal reaction that degrades the effectiveness of its own internal antitoxins, Wood explains. With its antitoxins damaged, the toxins present within the bacterial cell are left unchecked and damage the cell's metabolic processes so that it essentially shuts down, he adds. It's self-inflicted damage but with a purpose. "The cell normally doesn't want to hurt itself; it wants to grow as fast as possible," Wood states; the raison d'être for a cell is to make another cell," Wood says. "However, most bacteria have this group of proteins, and if this group was active - if you got rid of the antitoxins - this group of toxins would either kill the cell or damage it."

Specifically, Wood and his colleagues found that when encountering oxidative stress, their bacterial cells initiated a process through which an antitoxin called MqsA was degraded, in turn allowing the toxin MqsR to degrade all of the cells' messenger RNA. This messenger RNA, Wood explains, plays a critical intermediate role in the cell's process of manufacturing proteins, so without it the cell can't make proteins. With the protein-manufacturing factory shut down, the bacterial cell goes dormant, and an antibiotic cannot "lock on" to the cell. When the stressor is removed, the bacterial cells eventually come back online and resume their normal activities, Wood says.

It was the combination of the genetic studies at Texas A&M with our structural studies at Brown University that demonstrated that the proteins MqsR:MqsA form an entirely new family of toxin:antitoxin systems," Page says. "Remarkably, we have shown this system not only controls its own genes, but also many other genes in E. coli, including the gene that controls the response to oxidative stress."

This response mechanism, Wood emphasizes, does not replace the mutation-based approaches that have for years characterized cell behavior; it's merely another method in a multifaceted approach undertaken by bacteria to ensure survival.
"A small community of bacteria is in a sense hedging its bet against a threat to its survival by taking another approach," Wood says. "To the bacteria, this is always a numbers game. In one milliliter you can have a trillion bacterial cells, and they don't always do the same thing under stress.

"If we can determine that this 'going to sleep' is the dominant mechanism utilized by bacteria, then we can begin to figure out how to 'wake them up' so that they will be more susceptible to the antibiotic. This ideally would include simultaneously applying the antibiotic and a chemical that wakes up the bacteria. That's the goal - a more effective antibiotic."

**RNA Dynamics Deconstructed**

*ScienceDaily (Apr. 25, 2011) —* RNA plays a critical role in directing the creation of proteins, but there is more to the life of an RNA molecule than simply carrying DNA’s message. One can imagine that an RNA molecule is born, matures, and eventually, meets its demise. Researchers at the Broad have developed an approach that offers many windows into the lifecycle of these essential molecules and will enable other scientists to investigate what happens when something in a cell goes wrong. They describe their approach, which offers high resolution and a comprehensive scope, in a *Nature Biotechnology* article published online on April 24.

"People are discovering more and more how the RNA lifecycle is at the heart of problems we see in disease, but we actually understand a lot less about it than we understand about many other cellular processes," said Aviv Regev, a core faculty member of the Broad Institute and a co-senior author on the paper.

Regev and her colleagues have developed a method that allows them to tease apart the different stages of this lifecycle by measuring how much messenger RNA is produced and how much is degraded. The balance of these two processes contributes to the changes seen in RNA levels in a cell over time, much the way that birth and death rates contribute to a country’s total population.

RNA levels are dynamic -- they change in response to certain stimuli. For this study, the researchers examined dendritic cells, which are involved in the body's immune response, as a model. They exposed these cells to a stimulus that resembled a pathogen and then looked at RNA changes before and after exposure.

"We wanted to understand how cells regulate RNA levels, and if regulation happens at the step of producing the molecule, degrading the molecule, or processing it," said Michal Rabani, first author of the paper and an MIT graduate student at the Broad. "Each of these steps can affect the level of active RNA molecules in cells. If you want to understand what happens when things go wrong, you have to understand how things work when they work as they should."

The researchers’ approach allows them to look at a specific cell type and see changes in the expression of all genes. This combination of breadth and specificity offers a systematic view of how RNA changes over time. "If we want to look at specific neurons in the brain or a specific cell that’s lying between other kinds of cells in the lung, this technique allows us to zoom in on one process in one cell among a billion other cells. This is the case in many diseases, a short circuit in one specific cell type, and now we have a great tool to find it," said Ido Amit, a co-senior author of the paper and a scientist at the Broad.

The scientists harnessed an existing technique to trace the fate of newly produced RNA and paired it with a new sequencing-based technology that counts molecules of mRNA. The results also gave the researchers a view of some of the in-between steps, during which mRNA is edited or processed -- an unexpected but serendipitous finding. "That's the beauty of sequencing: it has a very extensive view so it shows you things you didn't expect to see," said Regev.

A key aspect of the approach is that the researchers were able to take "snapshots" of RNA levels over very short time intervals. Strung together, these snapshots reveal not only how the amount of RNA changes, but also the short-lived, intermediate phases of the RNA lifecycle that are otherwise impossible to detect. "This allows us many windows into the world of RNA," said Amit.

One critical application of the new method is in following up on leads from disease studies, such as mutated genes in cancer or other diseases that impact the RNA lifecycle. "In the past, you would know that there's a mutation and there's even a suspicion of what the gene does, but it would have been extraordinarily hard to see the effect of the mutation on these types of processes in the cell," said Regev, who is also an assistant professor at MIT and an early career scientist at the Howard Hughes Medical Institute. The researchers hope that their newly developed technique will enable others to gain deep insights into how gene mutations disrupt RNA levels, and in turn, what proteins are made.
“We’re decomposing these RNA levels, breaking them down into each separate step, so that we can understand what happens at each of these steps and how they interact with each other to produce the final read out,” said Rabani. “It’s a very complex system, but understanding it could eventually help us understand what goes wrong when things don’t work.”

**Journal Reference:**
Michal Rabani, Joshua Z Levin, Lin Fan, Xian Adiconis, Raktima Raychowdhury, Manuel Garber, Andreas Gnirke, Chad Nusbaum, Nir Hacohen, Nir Friedman, Ido Amit, Aviv Regev. *Metabolic labeling of RNA uncovers principles of RNA production and degradation dynamics in mammalian cells.* Nature Biotechnology, 2011; DOI: 10.1038/nbt.1861

One in eight European children with HIV experienced failure of three drug classes within five years

Carole Leach-Lemens  
Published: 26 April 2011

One in eight children and adolescents receiving HIV treatment at major HIV clinics in Europe experienced failure of three classes of antiretroviral drugs after five years of treatment, highlighting the need for formulations of new antiretroviral drugs to be developed that are suitable for children, European researchers report in *The Lancet*.

Triple-class failure implies that children has experienced the failure of at least two antiretroviral regimens, one containing a non-nucleoside reverse transcriptase inhibitor combined with a nucleoside analogue, and one containing a protease inhibitor combined with a nucleoside analogue. It also implies a degree of cross-resistance to other drugs in the same class.  

Children were twice as likely as adults with HIV in Europe to experience failure of their first antiretroviral regimen.

The PLATO II investigators for the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) reported a retrospective cohort study of 1007 children, among whom over one-third (33%) had started a third drug class after a median of 4.2 years (of which 105 (44% or 10% overall) were on a failing regimen).

About 25% of those who developed triple-class virological failure had never achieved viral suppression (a viral load measurement under 500 copies/mL).

The longer the children were on ART the greater the risk of triple-class virological failure: after five years the risk was 12% (95% CI: 9.4-14.6).

Approximately 2 million children are living with HIV, the majority infected through perinatal transmission. An estimated 700 children die every day because of AIDS-related causes. Without treatment an estimated 50% will die before they reach the age of two.

Antiretroviral therapy has dramatically improved the prognosis for HIV-infected children. Children have responded well to protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Guidelines now recommend starting treatment as soon as possible after HIV diagnosis.

Results from adults treated, in both resource-poor and resource-rich settings, with all three classes of antiretrovirals (PIs, NNRTIs and nucleoside reverse transcriptase inhibitors (NRTIs) suggest that long-term viral suppression is possible and virological failure happens slowly. It is unclear whether the same is true for children who will need to maintain viral suppression the longest.

The major challenge in treating children is to minimise virological failure and the development of drug resistance so that children will continue to have treatment options throughout adolescence and adulthood.

Alexandra Calmy and Nathan Ford from Médecins Sans Frontières in an accompanying Comment stress the potential difficulties for children, notably in resource-poor settings where 90% of HIV-infected children live: limited availability of current and effective treatment regimens, unclear strategies for the best drug sequencing as well as difficulties in maintaining good adherence from infancy to adulthood, all of which may contribute to drug resistance and virological failure.

The authors looked at the rate and predictors of triple-class virological failure to the three original drug classes in children.

From 1998 to 2008 in the COHERE the rate of triple-class failure was analysed in children under 16 years age infected perinatally who started antiretroviral therapy with three or more drugs. 1007 children from 14 COHERE cohorts were identified with over 90% from the UK and Ireland, Spain, Holland and France.
Triple-class virological failure increased over time, reaching close to 20% after eight years. The authors note that triple-class failure was highest in the first two years after having started ART and then rose slowly.

Calmy and Ford suggest these findings be understood in context. Close to a quarter of the children had started ART in 2000 when less effective regimens were in use and standardised treatment guidelines lacking.

However, Calmy and Ford note the findings give cause for concern. The overall virological failure rate is comparatively low. Nonetheless when the analysis is limited to children exposed to boosted PIs the cumulative proportion of failure is twice that of adults in the same cohort collaboration, 8.2% (95% CI: 5.1-11.2) compared to 4.2% (95% CI: 3.8-4.6) HR 2.2 (95% CI: 1.6-3.0, p<0.0001).

This raises the critical issue of treatment durability. Calmy and Ford add that no matter what the age the goal is to achieve and maintain sustained virological suppression. The fact that a significant number of children experiencing virological failure had never achieved virological suppression is disturbing, they add.

Reasons include: the complexities around adherence, particularly in very young children who depend on caregivers; very limited and often poorly adapted treatment options.

In young children and adolescents the authors note overlapping social issues: stigma, secrecy and guilt, disclosure as well as sexual development all contribute to poor adherence. Few studies, they add, have looked at these issues.

While they welcome the World Health Organization’s (WHO) efforts to issue user-friendly dosing tablets, Calmy and Ford express concern “that paediatric antiretrovirals are not currently a part of WHO’s work on priority medicines for maternal and child health.”

Calmy and Ford stress the urgency of developing new fixed-drug formulations for children. The absence of clinical data on the use of specific drugs in children hinders the process.

Calling upon researchers and drug developers to “prioritise the pursuit of paediatric indications for antiretroviral drugs” they note, “...children [notably in resource-poor settings] receive a lower standard of care than do adults.”

They conclude “The fact that the Drugs for Neglected Diseases Initiative...has recently included paediatric HIV/AIDS in its portfolio is telling: paediatric HIV/AIDS is a neglected disease.”

**References**


**FDA Says Merck Drug Successfully Fights Hepatitis**

Associated Press, (04.25.2011) Matthew Perrone

A Food and Drug Administration review found Merck & Co.’s new hepatitis C drug cures more patients in less time than current therapies, though some safety questions remain. FDA’s analysis was posted Monday ahead of a public meeting Wednesday on whether to approve boceprevir.

And on Thursday, a similar drug made by Vertex Pharmaceuticals Inc. will be considered by FDA’s panel. Both medicines are protease inhibitors, blocking an enzyme that allows hepatitis C virus to replicate. The tablets differ from the standard HCV treatments, ribavirin and interferon-alpha, which are designed to boost the immune system.

The two studies submitted by Merck show boceprevir patients had undetectable HCV levels six months post-treatment. Boceprevir plus standard treatment boosted cure rates to 60 percent-65 percent, compared with 40 percent for traditional HCV drugs alone. In addition, the studies indicate that adding boceprevir to standard HCV therapy helped cut treatment time in half, reducing exposure to the older drugs’ side effects.

But FDA scientists said some late-responding patients may need to take the boceprevir combination for eight months. In addition, African Americans were among other groups who should receive longer therapy. Blacks, who comprise 20 percent of persons with HCV, had a cure rate 15 percent-25 percent lower than other racial groups. FDA also questioned boceprevir’s efficacy in patients who have failed standard treatment.
Boceprevir was associated with an “increased frequency and severity of anemia,” FDA said, requiring further review. And though the agency found an increased number of reported symptoms of “suicidal and homicidal ideation” with boceprevir, FDA noted “it is difficult to make any meaningful clinical conclusion from this observation.”

FDA is scheduled to make a final decision on boceprevir in May. To access the agency briefing, visit: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM252341.pdf.

**Lack of Timely Treatment Raises Risk of Cancer**

*Inter Press Service*, (04.18.2011) Marcela Valente

Cervical cancer closely tracks poverty in Latin America, ranking as the most-frequent type of cancer among women in countries with the poorest populations. Chiefly caused by high-risk strains of human papillomavirus (HPV), the infection progresses to cervical cancer most often where women lack access to health services, said Dr. Marcia Moreira, an epidemiologist at the Pan American Health Organization (PAHO).

“If you look at a map of the world, breast cancer is predominant in rich countries and cervical cancer in the poorest countries,” said Moreira. “Prevention depends a great deal on women’s capacity to negotiate protection [in sexual relations], and on their access to information, health services, early diagnosis, and timely treatment.”

Cervical cancer is the most frequently diagnosed cancer for women in Bolivia, Guatemala, Honduras, Nicaragua, and Peru, and the second-most common - after breast cancer - in Argentina, Brazil, Colombia, Costa Rica, Ecuador, Mexico, Paraguay, and Venezuela, according to the International Agency for Research on Cancer.

About 40 percent of Latin America cancer diagnoses could be prevented by regular check-ups, exercise, healthy diet, and avoidance of tobacco and excessive drinking, PAHO says. Among poor women, cervical cancer is tied to lack of awareness, prevention, and control.

“Sometimes they get a Pap smear, but they don’t come back, and they aren’t informed of the result even if it’s bad,” Moreira said. “Women tend to be the last ones in the family to take care of themselves, and the health services don’t reach out to them.”

In Argentina’s least-developed, northwest provinces, the cervical cancer rate is almost four times that in Buenos Aires. Free HPV vaccine is now offered for girls ages 10-11 in high-risk areas.

“In Panama [the HPV vaccination] is massively administered; Costa Rica is considering it; and in Mexico it is being introduced experimentally, but it is a process that will have effects only in the long term,” Moreira said.

**University Shares $10 Million in Pursuit of New Weapon Against HIV**

*St. Paul Pioneer Press*, (04.18.2011) Christopher Snowbeck

University of Minnesota researchers will receive half of a $10 million National Institutes of Health grant to study innate antiviral proteins that, if boosted, may prevent HIV from replicating in human cells.

“Everyone has [these proteins], and several have the capacity to destroy HIV,” explained Rueben Harris, an associate professor of biochemistry, molecular biology, and biophysics. “The problem is that HIV and other viruses that are susceptible to [these proteins] have figured out ways to neutralize our innate immune responses.”

In 2008, Harris and colleagues discovered the APOBEC3G protein, one of several “APOBECs” that human cells produce naturally. That research showed how HIV binds to and destroys one of the proteins, suggesting that a relatively simple change to the chemical structure of APOBECs could boost their virus-fighting capabilities.

The researchers will use the grant to produce atomic resolution images of the proteins to better understand how they interact with HIV and other proteins in human cells. The goal is to find a way to prevent HIV from attaching to and entering cells, said Harris.

“People are just starting to come around to the fact that we have really powerful innate immune defenses that can kill the virus,” said Harris. “Now we need to understand how we can boost those defenses.”

**Outcry as Boys Sent to Anti-Gay Boot Camp**

*Australian Broadcasting Corporation News*, (04.20.2011)
Advocates in Malaysia are worried that anti-AIDS efforts could be hurt by the news that the Terengganu state education department has ordered 66 boys to an anti-gay boot camp. The youths, who were labeled effeminate by their teachers, are to spend a week at the camp undergoing physical and religious education, and listening to motivational speakers. “It’s crazy that the state itself is actively taking part in bullying and subjecting an already vulnerable group of students to further ridicule and torture,” said rights activist Pang Kee Teik. This could have a chilling effect on HIV prevention efforts, said Raymond Tai of the PT Foundation. “It’s getting difficult for us to do our outreach work at gay venues, as well as on the streets with sex workers and transgenders, simply because many of these people are very much underground now,” he said. “So it’s difficult for us to reach them, and even if we are able to reach them, there is a lot of harassment from the state authorities like the police, enforcement officers, religious officers.”

**Vertex’s Hepatitis C Drug Aces Review**
*Boston Globe*, (04.27.2011) Robert Weisman

Vertex Pharmaceuticals Inc.’s hepatitis C virus treatment results in a sustained virologic response in more patients and in less time than traditional treatment alone, according to a briefing document filed Tuesday by Food and Drug Administration staff members. Using FDA criteria, the regimen including Vertex’s telaprevir had a 79 percent SVR for patients. The HCV protease inhibitor is up for review by an FDA advisory committee on Thursday.

The brief notes two side effects reported by Vertex: anemia and skin rashes in some patients taking the three-drug combination regimen - telaprevir plus standard HCV drugs. The telaprevir-based drug cocktail proved more effective than the older drugs alone, which had a 46 percent SVR rate, the paper says.

The committee's daylong hearing on Thursday will center on whether to recommend approval of telaprevir, whose prospective brand name has not been disclosed. Founded in 1989, Vertex has been hiring hundreds of sales and marketing reps in anticipation of a launch.

Today the same FDA committee considers Merck & Co.’s HCV treatment boceprevir, which also inhibits the protease enzyme the virus needs for replication. Taken with other HCV drugs, boceprevir yielded an SVR for 66 percent of patients, according to an FDA briefing paper. Boceprevir also caused side effects in some patients, including anemia and blood disorders. If the drug is approved, Merck plans to market it as Victrelis.

For more information, visit www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/ucm252750.htm.

**Early Exposure to Parents' Relationship Instability: Implications for Sexual Behavior and Depression in Adolescence**
*Journal of Adolescent Health Vol. 47; No. 6: P. 547-554*, (12.2010) Kelly L. Donahue, BA; Brian M. D’Onofrio, PhD; John E. Bates, PhD; Jennifer E. Lansford, PhD; Kenneth A. Dodge, PhD; Gregory S. Petit, PhD

The current study examined the effects of the timing of parents’ relationship instability on adolescent sexual and mental health.

A total of 585 participants were assessed annually from age five through young adulthood as part of a multisite community sample. The timing of parents’ relationship instability and whether it was predictive of adolescents’ history of sexual partnerships (SP) and major depressive episodes was examined. Multivariate logistic regression analyses controlled for potential mediators related to parenting and the family, including parental knowledge of activities, parent-child relationship quality, number of parents’ post-separation relationship transitions, and number of on-hand caregivers.

Participants who experienced parents’ relationship instability before age five were more likely to report SP at age 16 (adjusted odds ratio=1.58) or an adolescent episode of major depression (AOR=2.61). Greater parental knowledge at age 12 decreased the likelihood of SP at age 16, “but none of the hypothesized parenting and family variables statistically mediated the association between early instability and SP or major depressive episode,” according to the study.

“These results suggest that experiencing parents’ relationship instability in early childhood is associated with sexual behavior and major depression in adolescence, but these associations are not explained by the parenting and family variables included in our analyses,” the authors concluded.
Needle Exchange Helps Cut HIV Rate: University Study Shows Changes Are Working

Montreal Gazette, (04.22.2011) Aaron Derfel

A new study finds Montreal’s needle-exchange programs (NEPs) have helped reduce HIV incidence rates among injecting drug users (IDUs).

The city was one of the first in North America to adopt harm-reduction strategies in the 1990s. However, a 1995 study showed that HIV incidence was higher among IDUs who used NEPs than among those who did not. Acting on that knowledge, the Montreal Public Health Department (MPHD) began making improvements to the programs, including doubling the number of syringes available. The new study suggests those enhancements are working.

In the prospective cohort study of the period 1992 to 2008, researchers at the Université de Montréal followed 2,137 IDUs who had tested HIV-negative at enrollment.

Annual HIV incidence rates declined four times faster after 2000, when IDUs started obtaining clean syringes from NEPs or supervised injection sites. In 2000, HIV incidence among IDUs was 5.1 per 100 person-years. By 2007, it had dropped to 0.4, before rising to 1.8 in 2008.

“The evolution of the policies has led to a reduction in HIV incidence,” said lead author Dr. Julie Bruneau. “Our study really shows that adapting services and opening new ways of reaching out to drug users that are at risk of HIV infection is the way to go.”

However, much more work is needed, said MPHD Director Dr. Richard Lessard. “The significant reduction of HIV transmission among [IDUs] constitutes a real, though insufficient step forward,” he said. “Since the early 2000s ... hepatitis C infection has taken on alarming proportions. During this period, the distribution of injection material has not attained the expected deployment, and for this reason, we have to increase our efforts.”


The VITROS Immunodiagnostic Products Anti-HIV 1+2 Assay (long)

A Rapid and Reliable Method for HIV Screening

Matthew P. Thompson, DO, MS; Darnely Hidalgo, MT(ASCP); Anne Kim, MT(ASCP); M. Qasim Ansari, MD


Abstract and Introduction

Abstract

Background: To ensure increased awareness of HIV status by patients, the Centers for Disease Control and Prevention (CDC) has issued new guidelines that greatly expand screening recommendations. The goal of the present study was to assess the overall reliability, sensitivity, specificity, and turnaround time (TAT) of the VITROS Anti-HIV 1+2 Assay (Ortho Clinical Diagnostics, Rochester, NY) in a large community hospital setting. The assay was recently approved by the Food and Drug Administration (FDA).

Methods: We compared our current Abbott HIVAB assay (Abbott Laboratories, Abbott Park, IL) with how the VITROS performed on the random access VITROS ECI/ECIQ System in a head-to-head comparison of 298 patient samples and a retrospective comparison of TAT over an 8-month period of utilization.

Results: Our data indicate that the VITROS is as sensitive (100%, n=298) and more specific (98% vs 83%) than the Abbott HIVAB and has a faster average TAT (156 minutes vs 1266 minutes).

Conclusions: Use of this rapid and reliable assay will lead to greater awareness of HIV status and, hopefully, a decrease in incidence of HIV disease.

Introduction

Since the inception of enzyme immunoassays (EIA) for the diagnosis of HIV, the sensitivity and specificity of these tests have been progressively improved. First-generation screening tests used unpurified HIV-infected human cell lysates for the HIV antigen preparation. Second-generation tests used relatively pure recombinant HIV antigens to reduce high false-positive rates. The reporter-linked secondary antibodies used in the first and second generation recognized only the serum immunoglobulin G (IgG) anti-HIV, thereby creating a “window” period in which individuals could be HIV test negative but disease positive.
Third-generation tests have reduced this "window" period by incorporating purified reporter-labeled HIV antigen as the method for secondary detection, thereby allowing for both IgG and immunoglobulin M (IgM) anti-HIV antibodies to be detected. Fourth-generation assays using additional HIV p24 antigen testing have recently been introduced and would reduce the window period even further.

While more patients are being tested for HIV today than in the past, the number of patients receiving their test results has not increased concurrently. Studies suggest that approximately one-third of patients do not return to receive the results of traditional HIV tests and thus remain unaware of their disease status.\textsuperscript{[4–6]}

In an effort to decrease the percentage of HIV-infected individuals who are unaware of their HIV status (an estimated 25\% of infected persons), the Centers for Disease Control and Prevention (CDC) issued guidelines for HIV testing in 2006 that included "routine" HIV screening for adolescents, adults, and pregnant women in all public and private health care settings.\textsuperscript{[7]} An expanded HIV screening program is only one variable in the equation to decrease the number of HIV infected individuals unaware of their HIV status. Not only must we test more individuals, but we must also report test results rapidly. Ideally we'll report results to the patient before he or she leaves the testing medical facility. Decreasing the turnaround time (TAT) between specimen collection and result reporting will undoubtedly increase the number of individuals who are aware of their HIV status while providing rapid results to clinicians caring for these patients. Previous studies have shown that after diagnosis of HIV disease, patients generally reduce their risky sexual behaviors. Thus, improved knowledge of HIV status has the potential to decrease the overall incidence of HIV disease.

There are several current FDA-approved methodologies to accomplish rapid TAT, including EIA testing procedures and point-of-care testing (POCT) methods. There have been several studies on HIV POCT that have shown increases in the number of HIV-status aware individuals.\textsuperscript{[4]} The CDC and other agencies have therefore recommended the use of POCT. However, routine POCT is not easy to set up and is hampered by numerous limitations, including psychological trauma to the persons performing the tests, staff reluctance to incorporate the procedure due to the risk of false-positive results, decreased sensitivity and specificity, and the increased time and manpower (and related costs) required.\textsuperscript{[4]}

At Parkland Memorial Hospital, our current method of HIV screening uses the third-generation Abbott HIVAB test (Abbott Laboratories, Abbott Park, IL) that is run in batch mode on the Abbott COMMANDER system. Our current protocol requires 3 to 30 hours for specimen processing and resultant data reporting due to the requirement for batch processing. The Abbott HIVAB has been at the forefront of HIV diagnosis for several years with a manufacturer's reported sensitivity and specificity of 100\% and 99.90\%, respectfully. In an effort to meet the current CDC guidelines and decrease the TAT while maintaining the sensitivity and specificity standards, we evaluated the VITROS Assay, a third-generation assay with a chemiluminescent detection method that can be performed on the random access analyzer VITROS ECi/ECiQ Immunodiagnostic System (Ortho Clinical Diagnostics, Rochester, NY). This assay has a manufacturer's reported sensitivity and specificity of 99.94\% and 99.70\%, respectively.

As part of our laboratory verification process, any new laboratory test is verified by stringent comparison with the standard method used in the laboratory. Our comparative evaluation focused on the sensitivity, specificity, and TAT obtained by the VITROS assay in comparison with the Abbott system. In this study, we present the results of our laboratory verification process comparing the 2 methods.

**Materials and Methods**

**HIV Screening Assays**

There were 298 representative serum samples tested on the Abbott assay using the manufacturer's instructions. The results were grouped into reactive (>2.2 OD), indeterminate (2–2.2 OD), and nonreactive (<2.0 OD). Briefly, according to the manufacturer's protocol, serum specimens were incubated with a polystyrene bead coated with recombinant HIV-1 env, and gag and HIV-2 env proteins, followed by a wash and addition of a horseradish peroxidase (HRP)-labeled conjugate. Next, o-Phenylenediamine (OPD) solution containing hydrogen peroxidase was added, and the intensity of the color developed was measured by a spectrophotometer (Figure 1).
Serum specimens from the same 298 individuals were then tested on the VITROS assay according to manufacturer’s instructions. The results were grouped into reactive (>1.0 s/c), indeterminate (0.91–1.0 s/c), and nonreactive (<0.9 s/c).

Briefly, according to the manufacturer’s instructions, serum specimens were incubated with HIV recombinant antigen coating the reaction well. Horseradish peroxidase-labeled recombinant HIV antigens were added with a conjugate reagent. The bound HRP conjugate was measured by a luminescent reaction. For both assays, all negative results were reported as such. For Abbott, all positive and indeterminate results were repeated in duplicate and confirmed by indirect fluorescent antibody (IFA). For VITROS, positive samples were not repeated.

**HIV Confirmation Testing**

An IFA test (Fluorognost HIV-1 IFA test, Sanochemia Pharmazeutika, Vienna, Austria) was performed according to the manufacturer’s protocol on all reactive and 20 negative specimens to detect/confirm the presence of HIV antibodies.

Briefly, according to the manufacturer’s instructions, diluted serum was placed on HIV1 infected and uninfected T-cell wells of the IFA slide and incubated. Unbound material was washed away followed by the addition of fluorescein isothiocyanate (FITC) conjugate and incubated again. The slides were then analyzed for a characteristic pattern of fluorescence.

**Average Time to Result Reporting**

The TAT was calculated as the time from specimen receipt in the laboratory until result reporting. This information was obtained from the computer-generated time stamps automatically created on specimen receipt and result reporting. The TAT data were obtained from an 8-month time period that bridged the transition from the use of the Abbott HIVAB to the VITROS ECi/ECiQ.

The time from the order for the HIV screen by the physician to specimen receipt in the laboratory were presumed to be equal for both methods and not included in the calculation of the TAT.

**Results**

**Comparison of Sensitivity**
A total of 298 samples were analyzed (n=298). The sensitivity was determined as the number of true positives divided by the true positives plus false negatives. The true positives were screen positive sera that tested positive by IFA. The false negatives were negative by the screening assay and positive by IFA. The Abbott and VITROS assays had no false negatives in our population, giving both tests a sensitivity of 100% (Table 1 and Table 2). Confirmatory IFA tests are not routinely performed on negative screening samples. Twenty negative samples by both methods were analyzed by the IFA confirmatory test, and all
were found to be negative. Based on this small study, the manufacturer's data, and published literature, we have assumed there are no false negatives for either method.

**Table 1. VITROS Anti-HIV 1+2 Results**

<table>
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<tr>
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<th>IFA Negative</th>
<th>IFA Positive</th>
<th>Totals</th>
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<tr>
<td>VITROS Anti-HIV 1+2 positive</td>
<td>3</td>
<td>148</td>
<td>151</td>
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<tr>
<td>VITROS Anti-HIV 1+2 negative</td>
<td>147*</td>
<td>0*</td>
<td>147</td>
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* = IFA was performed on 20 random negative specimens.

**Table 2. Abbott HIVAB Results**

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<th>IFA Negative</th>
<th>IFA Positive</th>
<th>Totals</th>
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<tr>
<td>Abbott HIVAB positive</td>
<td>31</td>
<td>148</td>
<td>179</td>
</tr>
<tr>
<td>Abbott HIVAB negative</td>
<td>119*</td>
<td>0*</td>
<td>119</td>
</tr>
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* = IFA was performed on 20 random negative specimens.

**Comparison of Specificity**

A total of 298 samples were analyzed (n=298). The specificity was determined as the number of true negatives divided by the true negatives plus false positives. The true negatives were the screen-negative sera found to be negative by IFA (150). The false positives were screen positive and negative by IFA. For the Abbott assay, 31 samples were reactive on screening but negative by IFA, yielding a specificity of 83% (Table 2). For the VITROS assay, 3 samples were reactive on screening but negative by IFA, yielding a specificity of 98% (Table 1).

**Table 2. Abbrev HIVAB Results**

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<th>IFA Positive</th>
<th>Totals</th>
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<td>148</td>
<td>179</td>
</tr>
<tr>
<td>Abbott HIVAB negative</td>
<td>119*</td>
<td>0*</td>
<td>119</td>
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**Table 1. VITROS Anti-HIV 1+2 Results**

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<tbody>
<tr>
<td>VITROS Anti-HIV 1+2 positive</td>
<td>3</td>
<td>148</td>
<td>151</td>
</tr>
<tr>
<td>VITROS Anti-HIV 1+2 negative</td>
<td>147*</td>
<td>0*</td>
<td>147</td>
</tr>
</tbody>
</table>

* = IFA was performed on 20 random negative specimens.

Our data show a slight reduction in specificity of both assays as compared with the manufacturers' published numbers. This is most likely due to the low HIV prevalence population tested in our study. Most patients at Parkland Memorial Hospital were pregnant women tested routinely during the second and third trimesters of pregnancy.

**Comparison of TAT**

The Abbott screening assay is performed in batch, and the processing consists of multiple steps and incubations (Figure 1) and requires greater than 3 hours of onboard analytic time. Up to 2 batch tests were performed each day. Each batch could include a maximum of 4 trays of 60 tests each. The VITROS screening assay is performed on a random access analyzer with minimal processing (Figure 2) with an onboard reaction time of approximately 48 minutes.
A total of 5271 specimens spanning 8 consecutive months were analyzed for TAT. The average TAT per specimen for the Abbott HIVAB screening assay ran in batch was 1266 minutes, while the average TAT per specimen for the VITROS ECi/ECiQ screening assay ran on a random access platform was 156 minutes (Figure 3).  

Figure 2. VITROS ECi/ECiQ screening assay workflow and processing.
**Data Breakdown**
- 119 samples were negative by both assays
- 148 samples were reactive by both assays and IFA positive
- 3 samples were reactive by both assays and IFA negative
- 28 samples were reactive by the Abbott assay but non-reactive by the VITROS assay and IFA negative
- 0 samples were reactive by the VITROS assay and non-reactive by the Abbott assay
- 0 samples were indeterminate by either assay

**Discussion**
The VITROS assay provided our laboratory with some clear advantages. It had the same low sensitivity as the reliable Abbott assay, giving us the same low false-negative rate, and it had an improved specificity rate of 98% compared with Abbott's 83%. The increase in specificity would lead to less frequent delays and fewer orders for IFA confirmatory assays.

There was also a huge advantage in TAT with our new VITROS assay. Because it is run on a random access analyzer, the VITROS assay outperformed the batch mode Abbott assay in TAT. The decreased TAT of less than 3 hours makes it possible for patients in Parkland Memorial Hospital's emergency room to know their HIV status prior to discharge. This will lead to better management of the patient’s disease and possible change in risky behavior, thus ultimately impeding the spread of disease in Dallas County, TX. This improved TAT will also facilitate appropriate treatment of an HIV-positive woman during labor if she is admitted with an unknown HIV status, thus leading to reduced incidence of vertical transmission to the infant.

Additionally, this benefit can now be achieved without having to undergo the cost and emotional stress of implementing a POCT system. By its nature, instituting a widespread program of HIV screening using the POCT is extremely challenging. For a busy county hospital like Parkland, which in 2009 had 1,131,000 outpatient visits and more than 108,000 emergency room visits, setting up a POCT program would be especially difficult. The VITROS assay helps us provide extremely rapid and reliable results, thus meeting the goals of the CDC’s new guidelines.

The philosophy of HIV screening assays has been traditionally more focused on increasing sensitivity and eliminating the risk of a false-negative result without putting much emphasis on specificity. However, given the recent cost-conscious environment, more emphasis is being placed on eliminating unnecessary
testing and developing more specific screening assays. The significant increase in specificity of the VITROS assay may result in cost savings for our laboratory via reduction of unnecessary confirmation testing of false-positive screening assays.

In summary, our evaluation of the Abbott and VITROS screening assays showed that the VITROS assay was superior in specificity and TAT while maintaining the high sensitivity we have come to expect from the Abbott assay.

We anticipate the decrease in TAT will result in many more patients becoming aware of their HIV status, leading to earlier treatment and risk stratification of our patient populations with and without HIV. Ultimately, we hope to see a decrease in the incidence and spread of HIV in Dallas County.

References

Non-Communicable Diseases Responsible For More Than Half Of Deaths Worldwide, WHO Report Says
Chronic and non-communicable illnesses, such as cancer, diabetes and heart disease, are at epidemic proportions and cause more deaths worldwide than all other diseases combined, the WHO said in a report released Wednesday, Reuters reports.

In its first global report on non-communicable diseases (NCDs), the WHO said 36 million, or 63 percent, of the 57 million deaths worldwide in 2008 were the result of such illnesses (Kelland, 4/27). Eighty percent of those deaths occurred in low- and middle-income countries, where they are a greater burden than infectious diseases, including HIV, tuberculosis and malaria, BBC News reports.

"For some countries, it is no exaggeration to describe the situation as an impending disaster; a disaster for health, for society, and most of all for national economies. Chronic non-communicable diseases deliver a two-punch blow to development. They cause billions of dollars in losses of national income, and they push millions of people below the poverty line, each and every year," WHO Director-General Margaret Chan said (4/27).

Cardiovascular disease, cancer, respiratory disease and diabetes account for approximately 80 percent of all NCD deaths and share the risk factors of tobacco use, physical inactivity, harmful use of alcohol and poor diets, according to a WHO press release. The report noted that national government policies to fight NCDs should include "stronger anti-tobacco controls and promoting healthier diets, physical activity, and reducing harmful use of alcohol; along with improving people’s access to essential health care," the release states.

The first-ever U.N. General Assembly high-level meeting on the prevention and control of NCDs is scheduled to be held in New York from September 19-20, 2011 (4/27).

Health Effects Of Chernobyl Nuclear Crisis Remain Unknown 25 Years After Incident
Though it has been 25 years since a disastrous explosion at the Chernobyl nuclear power plant in Ukraine sent radioactive material into the air, affecting Russia, Ukraine and Belarus, as well as the rest of the world, "experts are still debating the long-term health effects of the disaster," the Los Angeles Times' "Booster Shots" blog reports.

30 people died in the immediate aftermath of the explosion, several more died of radiation poisoning over the next decade, and in 2008, the U.N. released a report concluding that 6,000 cases of thyroid cancer among young people were linked to the disaster (Brown, 4/26).

Fred Mettler, a radiologist with a U.N. radiation study group, said the incident has caused about 7,000 cases of thyroid cancer, which is rare and known to be caused by exposure to radioactive iodine, NPR's "Morning Edition" reports. While most of these cases have been cured, more cases are expected.
"We don’t know whether that risk will go down over time or keep going up or level off. That's probably the biggest thing that will be studied and focused on," Mettler said (Joyce, 4/26).

"Institutional failure aside, attempts by the international research community to learn and implement the public health lessons of Chernobyl have been less than effective," according to a BMJ editorial, which calls for more study into the "long term health effects" of Chernobyl (Baverstock, 4/26).

The Union of Concerned Scientists has suggested "that excess cancers and cancer deaths worldwide will number in the tens of thousands, or even higher," because of radiation released from Chernobyl, according to "Booster Shots" (4/26). And a Lancet Oncology comment this week said exact numbers may never be known because of "considerable logistical challenges in doing epidemiological research in countries of the former Soviet Union," including "[l]ittle expertise in chronic epidemiology at the time, language barriers, cultural differences, and the daily challenges in covering a very large study area."

However, the authors added that the recent incident at the Fukushima Daiichi plant in Japan "sadly...offer[s] another opportunity to study the cancer consequences of accidents at nuclear power plants" because Japan has studied the effects of radiation for decades and has the ability to organize reliable epidemiological studies (Moysich et al., 4/26).

In a fact sheet on ionizing radiation, the WHO outlines its activities to study the health effects of Chernobyl and presents an FAQ fact sheet (.pdf) on the incident and its effects (4/23).

Symptoms of primary HIV infection often mistaken for malaria, representing missed opportunity for testing and prevention
Carole Leach-Lemens  
Published: 28 April 2011

Almost two-thirds of a cohort of Kenyans newly infected with HIV had sought treatment for fever, and 40% of these received presumptive treatment for malaria, but only 12% were tested for HIV, highlighting important missed opportunities for diagnosis and prevention of onward transmission, Eduard J Sanders and colleagues report in a prospective cohort study published in the advance online edition of AIDS.

Half of those treated were tested for malaria parasites; all were negative. Only six percent were suspected of having acute HIV infection; in spite of 25% having had a symptomatic sexually transmitted disease in the three months before an HIV diagnosis.

Many people within the first few weeks of HIV-infection (also known as acute HIV-1 infection or AHI) will experience a sudden onset of illness including: fevers, joint pains, headache, tiredness and rash. Many will seek care.

Identification of people with AHI presents an important public health opportunity.

Newly infected people are highly infectious and may account for a large number of new infections. Early diagnosis presents an opportunity for improved treatment and care as well as potential behaviour change.

It is common in resource-rich settings to seek urgent healthcare for these symptoms. However, the authors note that little is known about health care seeking behaviours in sub-Saharan Africa around the time of AHI.

Given the interest in using point-of-care tests for early diagnosis of AHI, the authors chose to look at healthcare seeking in patients diagnosed with AHI in Kenya.

In July 2005 a prospective open cohort of men and women at risk for HIV began in two research clinics in Kilifi district in Kenya. Men and women aged 18-49 years of age who reported transactional sex work or men having sex with men (MSM) were enrolled voluntarily. Volunteers were given either three-monthly or monthly (when receptive anal intercourse was reported) appointments.

Records covering clinical, counselling, treatment and laboratory work of all previously HIV-negative at-risk individuals who had seroconverted between July 2005 and October 2010 and had agreed to be a part of the AHI cohort were reviewed.

The cohort comprised a total of 72 volunteers (60 men and 12 women); 60% of whom had either p24-positive or RNA-positive or HIV-1 discordant rapid test before seroconversion.

Median age at seroconversion was 25 (IQR: 22-28) for men and 24 (IQR: 23-27) for women. Over half had secondary or higher education. 93% of men were bisexual or homosexual; 77% (55) of men and 17% (2) of women reported receptive anal intercourse.

Before diagnosis 75% (54) reported fever. 69% (50) sought urgent care for symptomatic illness; 84% of whom had symptoms within a month of the estimated date of HIV infection. 32% first sought care in a non-research facility.
Over a quarter sought urgent care more than once before HIV diagnosis.

Only one in four patients with fever was tested for malaria parasites, yet in spite of negative results was treated for malaria.

Malaria treatment was strongly associated with fever (aOR: 46, 95% CI: 3-725) and a non-research setting (aOR: 5, 95% CI: 3-64).

However the World Health Organization’s (WHO) revised malaria treatment guidelines state that treatment be given upon a confirmed diagnosis. Treatment based on clinical symptoms can be considered only when “parasitological diagnosis is not accessible.”

The authors stress the urgent need for continued education for front line health care workers as well as for researchers working in a research setting.

The identification of people with acute HIV infection at point-of-care services will facilitate treatment and care as well as HIV prevention interventions.

The authors propose that, together with improved clinician training, a risk score algorithm is developed to evaluate acute HIV infection in resource-poor settings where previously malaria was the most common cause of fever.

The authors note that among research staff there was low recognition of AHI in spite of patients presenting with known predictors of HIV infection: symptomatic sexually transmitted infections and discordant rapid HIV test results before seroconversion.

While HIV is only one of many causes of fever in sub-Saharan Africa, the authors note they couldn’t determine whether testing for HIV was done at non research facilities but suspect it was not.

Limitations include the selection of a high-risk group; bias in recall; and differences in follow-up may have influenced estimated differences in illnesses in men compared to women.

The authors conclude the majority of adults with AHI in malaria-endemic areas seek urgent health care and most are treated presumptively for malaria. Improved recognition of AHI presents a public health opportunity for early diagnosis, treatment and care as well as improving HIV prevention strategies.

Reference

North Dakota Lawmakers Endorse Abstinence in Sex Education
Associated Press , (04.27.2011) Trevor Born
On Tuesday, state legislators passed a bill ordering schools to devote “a portion” of health curricula to teaching the benefits of abstinence from sex outside of marriage. Approval of the one-sentence measure took three weeks and a dozen meetings.

Health classes must expose students to the “social, psychological, and physical health gains” of avoiding sex outside marriage, according to language arrived at by Senate and House negotiators. The House approved the bill 81-12 on Tuesday, with the Senate following 43-4. It now heads to Gov. Jack Dalrymple.

“The intent is to try to focus on how important it is to stay away from those activities, rather than looking back in hindsight and trying to correct those problems they may have caused,” said Sen. Larry Luick (R-Fairmount).

“This kind of health care teaching has been going on in our state and across the country for a very long time,” said Sen. Connie Triplett (D-Grand Forks). “We are not reinventing the wheel here,” but adding “just an unnecessary layer of value judgment,” she said.

The head of the joint conference committee, Rep. RaeAnn Kelsch (R-Mandan), commended the message of fidelity in marriage. “This sends a much stronger, louder message, and probably more true to the facts,” she said. “Once you’re married, it doesn’t mean that abstaining from outside issues goes away, and children should be taught that.”

Luick had suggested that an infidelity focus might complicate the message. “We want to be focusing on things that are relevant to what they’re experiencing at the age they’re at,” he said.

Massachusetts Lawmakers Say Sex Education Website 'Disgusting'
On Tuesday, state Department of Public Health officials said they are receptive to discussing changes to a teen sexual health website that some legislators criticize as graphic and crude. A group of state lawmakers has sent Gov. Deval Patrick a letter asking that state funding be cut for www.mariatalks.com. The independent AIDS Action Committee maintains the site with a $100,000 annual DPH grant.
The website features “Maria” and other invented teen and adult characters who discuss subjects including sex, STDs, pregnancy, birth control, and abortion. Critics object to the site’s use of slang terms, its descriptions of sex acts, and the information it provides on abortion.

“Gov. Patrick, take down this website,” Rep. Marc Lombardo (R-Billerica) said at a news conference attended by about 20 lawmakers from both parties. “This website describes abortion in an extremely insensitive manner, downplays the medical and psychological damages, and advises teenage girls on how to circumvent parental notification requirements,” he said.

“The language that is used on this site is disgusting,” said Rep. Elizabeth Poirier (R-North Attleborough).

Defending the website, Rep. Byron Rushing (D-Boston) said its information is useful, and it “speaks the language that teenagers speak.”

A DPH statement said the agency is willing to meet with critics in the coming days and improve the site’s content, if needed. However, the website’s goal is to make accurate health information publicly available, and it remains “an important tool to help us do that,” DPH said.

The site’s supporters note that it includes a long section on abstinence, as well as information about adoption as an alternative to abortion.

**Calling India’s Sex Workers**

*New Scientist, (04.23.2011) Anil Ananthaswamy*

Thanks to an innovative new outreach, sex workers in Bangalore are receiving important health reminders via automated cell phone messages.

Many Bangalore sex workers are migrants from rural India and are easy prey to men who will pay more for condomless sex. The advocacy group Project Pragati (“progress”) was formed in 2005 by sex workers and for sex workers, after a study found that 12.5 percent of them were HIV-positive. In addition to advice on matters such as health issues and violence prevention, the project assists women by making small loans.

Three individuals - Nithya Sambasivan of the University of California-Irvine, and Julie Sage Weber and Edward Cutrell of Microsoft Research India - came up with a way for Project Pragati to reach sex workers with reminders to get tested for STDs, take their medicine, and make their scheduled loan payments. Recognizing that 97 percent of Bangalore sex workers have cell phones, they used the open-source telephony software Asterisk to contact them via recorded messages.

The calls are placed between 4 and 7 p.m., hours when both day and nighttime sex workers are likely to have their phones switched on. Because many of the women hide their sex work from their families, discretion is key: The messages reference blood tests and health exams, avoiding any mention of HIV or STDs, in case a relative picks up the phone. The use of voice, instead of text, messages in the local languages bypasses concerns about low literacy.

Research shows a high level of participation. The 31-second health care calls were picked up by 90 percent of the women, with almost 60 percent listening to the full message. Ninety-five percent picked up the 13-second finance message, and 90 percent listened to all of it.


**1918 Influenza Pandemic (Spanish Flu): Large Differences in Mortality Between Urban and Isolated Rural Areas**

*ScienceDaily (Apr. 27, 2011) — In urban communities, less than 1 in 100 inhabitants died from Spanish flu in 1918, but in isolated communities up to 9 out of 10 died. An important explanation for the differences is due to different exposure to influenza in the decades before the Spanish flu came. Those living in urban communities probably had a higher degree of pre-existing immunity that protected against illness and death in 1918 than those living in very isolated rural areas. This is shown in a new study from the Norwegian Institute of Public Health. Previous studies have suggested that an important reason for the large regional differences in mortality must be that people living in cities were more frequently exposed to similar viruses to the one that caused the Spanish flu earlier in life than those living in rural and extremely isolated areas. "It is not inconceivable that there was a different geographical spread of the virus in the 1800s and early 1900s, at a time when intercontinental communication networks were less developed” said Svenn-
Erik Mamelund, a senior adviser in the Division of Infectious Disease Control at the Norwegian Institute of Public Health.

"No one knows exactly which influenza viruses circulated before 1918. But a leading theory is that there were H1-like viruses circulating in the period before the last major pandemic, the Russian pandemic of 1889-90. Some viruses circulating prior to 1889 may therefore have been related to the virus that caused the Spanish flu in 1918, A (H1N1). This would mean that some people who were older than 28-30 years in 1918 may have had some protection against severe infection and death from Spanish flu because of previous exposure to similar viruses," he said.

**First to confirm anecdotal information from 1918 with quantitative data**

Analyses of age-specific mortality in urban and Western society in 1918, subtracted the expected mortality from seasonal influenza a few years before 1918, show that young adults had relatively high mortality, and those who were older than 65 years were largely spared. However, similar analyses for isolated communities, such as in Labrador, Canada, and Alaska, USA, showed that mortality for all adults over 30 years was very high, and up to 90-100 per cent.

"Data from church records for Okak, Hebron, and Brevig also supported the historical anecdotes about the high mortality in these isolated communities," said Mamelund.

The study also shows that it was mainly people belonging to indigenous populations who died in the worst affected areas. Findings suggest, that to a greater extent, the geographically isolated indigenous groups had risk factors associated with influenza, such as co-morbidities e.g. pulmonary tuberculosis, cramped living conditions and poverty compared to Caucasian populations living in cities and countries with a high degree of urbanisation in the West. In addition, loss of caregivers due to high mortality was an indirect cause of many fatalities. Genetic explanations may also have played a role, says Mamelund.

The study is published in the latest issue of the Epidemics journal, and is based on quantitative data from archives and church records and ethnographic data from Scandinavia, North America and Oceania.

**What conclusions can be drawn from this study?**

"Firstly, the new research shows that it was only in cities and countries in the West that people older than 65 years had lower than expected mortality. In very isolated indigenous communities, mortality was very high for all adults over 30 years of age, and higher than during seasonal outbreaks of influenza in the years before 1918.

"Secondly, we conclude that without adequate immunological protection for large parts of the world's population, Spanish flu would probably have claimed many more lives than the most widely quoted estimate of 50-100 million dead.

"Mortality rates during the recent A (H1N1) pandemic in 2009 were lower than during normal seasonal influenza. This may be partly due to similar mechanisms that were at work in 1918 also being in operation in 2009. Those who are older than 65 years usually have the highest mortality associated with seasonal influenza, but because of pre-existing immunity, few elderly people became ill and died in 2009. Serological studies from Europe, Japan and the USA. have shown that pre-existing immunity was highest among those born before 1918, but also those born later had some protection. Those born after 1949 had little or no immunity against the A (H1N1) virus in 2009."

**Do historical studies have relevance for future pandemic preparedness?**

"Yes, both historical and contemporary studies of the immune status and mortality during influenza pandemics for different ages and countries are important. The studies show that models of morbidity and mortality for future pandemics should include the significance of pre-existing immunity," concluded Mamelund.

**Journal Reference:**


**Indigenous Cases of Leprosy Found in the Southern United States: Human Contamination Through Contact With Armadillos**

ScienceDaily (Apr. 28, 2011) — Using advanced DNA analysis and extensive field work, an international research team has confirmed the link between leprosy infection in Americans and direct contact with armadillos. In a joint collaboration between the Global Health Institute at EPFL in Switzerland and Louisiana State University, clear evidence was found that a never-before-seen strain of *Mycobacterium leprae* has emerged in the Southern United States and that it is transmitted through contact with armadillos carrying the disease. The results will be published on April 28th in the *New England Journal of Medicine.*
There are only around 150 cases of leprosy in the United States each year. Most of these victims have worked abroad in areas in which leprosy is endemic, making it likely that they may have acquired the disease while outside the US. But, to the alarm of health authorities, a third of all patients infected appear to have contracted the disease locally. The hypothesis that the disease is transmitted through contact with armadillos -- aside from humans, the only other known carriers of the leprosy-causing bacteria -- was confirmed by fine-grained DNA analysis of both armadillo and human samples done at EPFL.

**Leprosy bacilli found in armadillos**

It has been known since the 1970s that armadillos are potential carriers of the disease, most likely introduced by European immigrants 500 years ago. But the current study shows inter-species contamination and the presence of a unique strain. "There is a very strong association between the geographic location of the presence of this particular strain of *M. leprae* and the presence of armadillos in the Southern US," explains Stewart Cole, head of the Global Health Institute in Lausanne and world-leader in the field of genomics of leprosy bacilli. "Our research provides clear DNA evidence that the unique strain found in armadillos is the same as the one in certain humans."

The study included 33 wild armadillos known to have the disease and 50 leprosy patients. The new strain of the bacteria, named 3I, was found in 28 armadillos and in 22 patients who reported no foreign residence. The researchers used genome sequencing to identify the new strain and cross check it with other known strains from Europe, Brazil and Asia, and used genotyping to identify and classify the population infected. It became clear that leprosy patients who never travelled outside the US but lived in areas where infected armadillos are prevalent were infected with the same strain as the armadillos. These findings prompted the researchers to state in the article that "Frequent direct contact with armadillos and cooking and consumption of armadillo meat should be discouraged." The study also suggests that armadillo range expansion should be monitored.

It is not known exactly why armadillos contract and carry leprosy. While their low body temperature (89° F / 32° C) makes them perfect incubators for the bacteria, which grow in temperatures between 86° F and 89° F (30° C to 32° C), there are almost certainly other factors such as immune deficiency that also play a role. Similarly, the bacteria attack the extremities of humans because our core body temperature is too high for a generalized infection, and over 90% of humans who come into direct contact with the disease spontaneously fight it off. "The last thing we want is to induce panic in the population and incite a slaughter of armadillos. The best way to combat further infection is though education and prudence," says Cole.

**The stigma of leprosy**

José Ramirez, a former migrant worker from Houston who contracted the disease after hunting and eating armadillo meat and took part in the study, has consecrated his life to combating social stigmas. He hopes that the study brings to light the stigma attached to leprosy. "We need to take this opportunity to give leprosy patients a voice and to learn to not use the word 'leper' that has negative connotations around the world, a stigma that should be replaced with an understanding of the disease and its causes." Ramirez, who struggled over five years with the disease before it was properly diagnosed, is now disease-free after receiving antibiotic treatment. Proving what few know to be true -- that leprosy is a bacterial infection that can be cured.

**Journal Reference:**

**Silent Epidemic**

**Why isn’t there a global movement to combat noncommunicable diseases?**

Jake Marcus

April 29, 2011 | 12:00 am

In Moscow on Thursday, health ministers from around the world gathered to discuss a serious global health crisis: the rise of non-communicable diseases (NCDs) like heart disease, stroke, depression, and cancer. Their goal is to replicate the successes of a similar meeting held nearly a decade ago, when the United Nations General Assembly convened a special session to combat HIV/AIDS. Since that session, development assistance for the disease has skyrocketed (from $960 million in 2001 to over $6 billion in 2008), and over 5.2 million people in developing countries now receive antiretroviral therapy. The global movement against HIV/AIDS imagined then has in many ways come to fruition, but don’t expect the campaign against NCDs to garner nearly the same level of support.
NCDs cause over 60 percent of the world’s deaths, yet, up to this point, the development community has largely neglected them. The United Nations Millennium Development Goals, for instance, have driven an ambitious global health agenda to improve child health, reduce maternal mortality, and combat infectious diseases like tuberculosis, malaria and HIV/AIDS. The goals, however, leave out any mention of NCDs. Investments in their prevention and treatment has paled in comparison to other areas of global health. Funding is so paltry that the international reporting system of the Organization for Economic Cooperation and Development (OECD), which collects data on foreign aid for health from donor countries, does not even have a code to track investments in NCDs.

Why this neglect? Part of the problem is the outdated worldview that NCDs are “diseases of affluence,” primarily affecting rich countries that have conquered infectious disease with improved sanitation, mass vaccinations, and better medical care. In reality, many developing countries today suffer from the double burden of infectious diseases and NCDs. Across countries in Africa in 2004, for instance, 2.8 million people died of NCDs—roughly the same number who died of HIV/AIDS, tuberculosis, and malaria combined. The World Health Organization (WHO) has estimated that obesity now kills nearly as many people in developing countries as being underweight does. High blood pressure, in that same analysis, topped a list of the health risks that accounted for the most deaths in developing countries, outranking unsafe sex, micronutrient deficiency, and poor water, hygiene, and sanitation.

Other practical constraints will also work against a coherent push to tackle NCDs after Thursday’s Moscow meeting. In 2001, advocates for a movement against HIV/AIDS had the luxury of focusing on just one disease. Today, health ministers must build a plan for combating a constellation of diseases and ailments ranging from heart disease to stroke to cancer to mental disorders. A wide range of interventions must be considered, including, among many others, cognitive behavior therapy for depression, increased screening for cervical cancer, and glycemic control programs for diabetics. Then, there’s the question of prevention. HIV/AIDS has one pathway for transmission—the exchange of bodily fluids—and usually requires only one event (one unsafe sex act or injection) to lead to infection. NCDs, by contrast, build up over years, even decades of exposure to poor diet, a sedentary lifestyle, a polluted environment, or other dangerous factors. As hard as it is to convince people to have safe sex, it may be harder to get people to commit to big lifestyle changes like eating and drinking less.

What’s more, there are emotional factors. HIV/AIDS strikes mostly young people, while NCDs largely affect people who are older. The image of a 50-year-old smoker and alcoholic with heart disease in Africa just doesn’t draw the kind of attention or money that an innocent 15-year-old infected with HIV/AIDS does. Finally, there is the fear factor. HIV/AIDS is infectious. If more people have it, it stands to reason that you have a higher chance of getting it. The rise of NCDs simply doesn’t stoke that kind of personal concern.

Successfully overcoming these hurdles will require a number of steps designed to concretize possible approaches to the diffuse problem of NCDs. Some of these are already underway; for instance, organizers for the Moscow meeting have incorporated strategies outlined by the WHO Framework Convention on Tobacco Control and the Global Strategy on Diet, Physical Activity and Health, a set of guidelines adopted by member states in 2004 to promote healthy behaviors, into the recommendations that they will propose to heads of state at a later U.N. meeting. The Moscow group has also reined in the complexity of the situation by identifying a set of priority diseases, risk factors, and interventions. The meeting intends to focus primarily on heart disease and stroke, diabetes, cancer, and chronic lung disease—still no small amount to cover—while a series of panels will address each of the four major risk factors for NCDs: tobacco, unhealthy diet, alcohol abuse, and physical inactivity. And the meeting will advocate for an intersectoral approach to NCDs, one that includes health systems as well as ministries of finance, agriculture, and even transportation.

Still, the fact remains that it will be an enormous uphill struggle to overcome the many political and practical challenges facing a movement to tackle NCDs in the developing world. The Moscow meeting and what comes out of it will be the world’s best shot to date. Given the potential impact of such a movement, we can only hope that policymakers beat the odds.

**USAID Response Fails to Condemn Laws that Criminalize HIV**

**Does USAID support laws that criminalize HIV?**

In February, the *Update* published a piece about how the U.S. government had pumped $35 million into a USAID program that produced a model HIV criminalization law in Africa.
We know these laws typically backfire, discouraging testing and putting many at risk of unjust persecution. In fact, when we wrote the piece, Robert Clay, the director of USAID's Office of HIV/AIDS, told us the U.S. government opposes laws that criminalize HIV non-disclosure.

We were curious about this contradiction—USAID is putting its money in one place but its words in another—and asked Clay to provide more information on the federal government’s stance on the criminalization of HIV. 

Read Clay’s response, which is posted on USAID’s Impact blog. 

Unfortunately, his response fails to clarify USAID’s position on laws that prosecute HIV non-disclosure. In fact, the words “criminal” and “law” never even appear in the response. Nor does his post provide any concrete examples of programs that combat HIV criminalization.

“The statement provided sounds like cowardly bureaucratese for ‘We’re not touching that with a ten foot pole,’” said Sean Strub, senior advisor to the Center for HIV Law and Policy’s Positive Justice Project. “Where’s the [USAID] funding for a conference on how dangerous these statutes are, how profoundly they drive stigma, [a conference] providing resources for combating and overturning them? When will that conference be held, funded by USAID?”

Immigration officials have turned HIV patients into prisoners, claims hospital

NHS consultants say that the UK Border Agency’s security measures have turned Hillingdon hospital into a prison

Diane Taylor
guardian.co.uk, Friday 29 April 2011 21.00 BST

HIV patients at a London hospital have in effect been imprisoned following a move by immigration officials to secure the sexual health unit, NHS consultants claim.

Hillingdon hospital in west London treats detainees at two immigration removal centres near Heathrow alongside other patients. The problems began when doctors refused to treat an HIV-positive detainee because the guard to whom he was handcuffed refused to uncuff him. An incident report was filed and sent to the medical director.

Officials from the UK Border Agency then installed restraints on the windows at the hospital’s sexual health clinic to ensure that detainees could not escape.

HIV specialist Ben Holden, a consultant at the hospital, said: “The unit is now a prison for us all. Our windows only open two inches but UKBA have installed chunky locks on them. We were told they would bring removable window restraints but these are permanent.

"No detainee has ever absconded or attempted to abscond. As doctors we believe that to keep immigration detainees restrained or locked in is discriminatory. I don't want to be part of a process that treats people in a less than human way."

Doctors are angry that immigration detainees who have committed no crime, approximately half of whom are later released, are treated in this way.

An audit conducted by the hospital revealed that none of the detainees removed from the UK were dispatched with a full three month supply of anti-retroviral drugs (in accordance with British HIV Association/National Aids Trust guidelines) because in many cases doctors at the hospital were not notified by UKBA prior to their removal. UKBA frequently cancelled appointments and some HIV-positive patients were removed before they were seen at the hospital.

Professor Jane Anderson, chair of the British HIV Association, said: "BHIVA and the National Aids Trust have developed advice on appropriate HIV treatment and care for people in the immigration removal system, and we are disappointed to hear that this advice is not always being followed. We want to see the highest standards of care for everyone with HIV in the UK. Any factors that make the provision of high quality clinical care difficult give us cause for concern."

Emma Ginn, co-ordinator of the charity Medical Justice – which recently published Detained and Denied, a report cataloguing examples of poor medical treatment for HIV-positive detainees – said: "Along with the potentially lethal medical abuse they suffer in detention centres detainees are suffering sub-human conditions in hospital."

The UK Border Agency said: "We have agreed the installation of window locks for detainee treatment with Hillingdon hospital and are working with them to address the concerns now raised. Detainees are only handcuffed when absolutely necessary and they are not handcuffed during treatment.
"The welfare of detainees is important but this must always be balanced with the security of the detainees and the public. Detainees have round-the-clock access to healthcare services to discuss their medication needs."

A spokesman for the Hillingdon hospitals NHS foundation trust said: "The UK Border Agency has told us that they do not believe our open ward environment is suitable for the treatment of individuals who may be failed asylum seekers and under restraint. However, a large proportion of the patients who are brought to our sexual health department by the agency are later discharged into the community and are not subject to the criminal law.

We have agreed a temporary measure with the Border Agency to put discreet bars on windows in the unit, but we are continuing to negotiate an agreement with the agency that will offer a solution that allows us to treat all our patients with respect."

**EDs should be aware of sexually transmitted infection risk in patients**

**One-quarter of symptomatic adolescent females tested positive for an STI**

DENVER – All adolescent females who show up in the emergency department (ED) complaining primarily of lower abdominal pain and/or urinary or genital symptoms should be tested for sexually transmitted infections (STIs), according to the authors of a study to be presented Saturday, April 30, at the Pediatric Academic Societies (PAS) annual meeting in Denver.

Previous studies have shown that when adolescents seek treatment for symptoms suggestive of an STI, they are not always tested, partly because health care professionals may not be aware of the risk of STIs in these patients. If not identified and treated, STIs can have serious long-term consequences such as infertility, ectopic pregnancy, chronic disease and death in babies, and cervical cancer. The presence of an STI also can increase the likelihood of acquiring HIV.

Researchers, led by Monika Goyal, MD, sought to determine how common STIs are in symptomatic adolescent females. Over the six-month study period, 236 females ages 14-19 years who sought treatment at a pediatric ED for symptoms of lower abdominal, pelvic or flank pain and/or genitourinary complaints were tested for three of the most common STIs: Neisseria gonorrhoeae, Chlamydia trachomatis and Trichomonas vaginalis.

Results showed that 26.3 percent of the patients had an STI. The most common was chlamydia (20 percent), followed by trichomoniasis (10 percent) and gonorrhea (3.5 percent). In addition, 19 percent of patients infected with chlamydia also had trichomoniasis, while 6.7 percent had both chlamydia and gonorrhea.

"Adolescents represent a high-risk group for sexually transmitted infections, and many providers are unaware of this association and the consequences that potentially occur due to infection," said Dr. Goyal, instructor of pediatrics and attending physician in the Department of Pediatrics, Division of Emergency Medicine, Children's Hospital of Philadelphia, University of Pennsylvania.

In addition, other studies have shown that adolescents often do not have a primary care doctor and go to the ED for medical care instead.

"Therefore, ED providers should be assessing STI risks in adolescents who come to the ED for care, as this may be the only point of contact of these patients and an opportunity to intervene," Dr. Goyal said.

**Antibiotic-Resistant Bacteria Have Evolved a Unique Chemical Mechanism, New Discovery Reveals**

ScienceDaily (Apr. 29, 2011) — For the first time, scientists have been able to paint a detailed chemical picture of how a particular strain of bacteria has evolved to become resistant to antibiotics. The research is a key step toward designing compounds to prevent infections by recently evolved, drug-resistant "superbugs" that often are found in hospitals, as well as in the general population.

A paper describing the research, by a team led by Squire Booker, an associate professor in the department of chemistry and the department of biochemistry and molecular biology at Penn State University, will be posted by the journal Science on its early-online Science Express site on 28 April. This paper is a continuation of research led by Booker published in another paper in Science earlier this month.

The team began by studying a protein made by a recently evolved "superbug." Booker explained that, several years ago, genetic studies had revealed that Staphylococcus sciuri -- a non-human bacterial pathogen -- had evolved a new gene called cfr. The protein created by this gene had been found to play a key role in one of the bacterium’s mechanisms of antibiotic resistance. Later, the same gene was found to have crossed over into a strain of Staphylococcus aureus -- a very common kind of bacteria that constitutes part
of the flora living in the human nose and on the skin, and which is now the cause of various antibiotic-resistant infections. Because this gene often is found within a mobile DNA element, it can move easily from a non-human pathogen to other species of bacteria that infect humans.

"The gene, which has been found in *Staphylococcus aureus* isolates in the United States, Mexico, Brazil, Spain, Italy, and Ireland, effectively renders the bacteria resistant to seven classes of antibiotics," Booker explained. "Clearly, bacteria with this gene have a distinct evolutionary advantage. However, until now, the detailed process by which the protein encoded by that gene affected the genetic makeup of the bacteria was unclear; that is, we didn't have a clear 3D picture of what was going on at the molecular level."

To solve the chemical mystery of how such bacteria outsmart so many antibiotics, Booker and his team investigated how the Cfr protein accomplishes a task called methylation -- a process by which enzymes add a small molecular tag to a particular location on a nucleotide -- a molecule that is the structural unit of RNA and DNA. When this molecular tag is added by a protein called RlmN, it facilitates the proper functioning of the bacterial ribosome -- a gigantic macromolecular machine that is responsible for making proteins that bacteria need to survive. Many classes of antibiotics bind to the ribosome, disrupting its function and thereby killing the bacteria. The Cfr protein performs an identical function as the RlmN protein, but it adds the molecular tag at a different location on the same nucleotide. The addition of the tag blocks binding of antibiotics to the ribosome without disrupting its function.

What had perplexed scientists is that the locations to which RlmN and Cfr add molecular tags are chemically different from all others to which tags routinely are appended, and should be resistant to modification by standard chemical methods," Booker said. "What we've discovered here is so exciting because it represents a truly new chemical mechanism for methylation. We now have a very clear chemical picture of a very clever mechanism for antibiotic resistance that some bacteria have evolved."

Booker also said he believes the next step will be to use this new information to design compounds that could work in conjunction with typical antibiotics. "Because we know the specific mechanism by which bacterial cells evade several classes of antibiotics, we can begin to think about how to disrupt the process so that standard antibiotics can do their jobs," he said.

**Journal Reference:**

### How Do White Blood Cells Detect Invaders to Destroy?

**ScienceDaily (Apr. 29, 2011) —** Scientists at Cedars-Sinai Medical Center have discovered how a molecular receptor on the surface of white blood cells identifies when invading fungi have established direct contact with the cell surface and pose an infectious threat.

The receptor called Dectin-1, studied in the laboratory of David Underhill, PhD, an associate professor in Cedars-Sinai’s Inflammatory Bowel and Immunobiology Research Institute, detects fungi and instructs white blood cells whether to expend the energy needed to devour the invading pathogens. The findings are featured as the cover story in the April 28 edition of *Nature*.

Although scientists long have theorized how immune cells recognize microbial debris sloughed from invading organisms at some distance from themselves, this study establishes a model to explain how immune cells determine when pathogens are directly in contact with their surface and thus pose a significantly greater risk, demanding rapid destruction.

The study is important because it moves scientists one step closer to understanding the mysteries of how our bodies mount an immune response to fight disease.

In early stages of infection, white blood cells patrol the body looking for invading pathogens. Dectin-1, a receptor on the surface of white blood cells, recognizes specific components of fungal cell walls, and alerts or "switches on" the immune cells to prepare to fight the infection.

"Our lab has been studying Dectin-1, which directs white blood cells to eat and kill the fungi that they encounter directly, but to ignore soluble material sloughed off of the fungal surface which does not pose an immediate threat," said Helen Goodridge, PhD, first author on the study and a researcher in the laboratory headed by Underhill. "This is important because phagocytosis and anti-microbial defense responses are energy-intensive and destructive, and should only be used when absolutely necessary."

During phagocytosis, a white blood cell encounters a microbe, engulfs it, and eats it. Once inside the cell, the microbe can be killed using a combination of degradative enzymes, highly reactive chemicals, and an acidic environment.

A molecular structure that the Underhill lab calls a "phagocytic synapse" forms at the surface of the white blood cell when Dectin-1 detects fungi. As a phagocytic synapse forms, two inhibitory proteins that
block transmission of signals inside the white blood cell are pushed aside. This allows Dectin-1 to instruct the cell to respond. The phagocytic synapse does not form when Dectin-1 encounters soluble fungal debris, so the white blood cell does not respond.

"The phagocytic synapse resembles another molecular structure, the 'immunological synapse.' It is critical at later stages of an immune response," said Underhill. "It appears that the phagocytic synapse may be an evolutionary precursor of the immunological synapse."

**Journal Reference:**