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Teen 'Sexual Activity' Bill OK’d

Knoxville News-Sentinel, (04.30.2012) Tom Humphrey
The Tennessee Senate on Friday approved a House amendment to SB 3310, sending the sex education guidelines bill to the governor for consideration.

Under the measure, classroom instructors who promote or condone “gateway sexual activity” are subject to a $500 fine. The bill says “gateway sexual activity means sexual contact encouraging an individual to engage in a non-abstinent behavior.” Some lawmakers objected to that language, calling it unclear. “Gateway sexual activity is so vaguely defined it could be holding hands, hugging, anything that teenagers do like that,” said Rep. Mike Steward (D-Nashville).

The bill’s sponsor, Rep. Jim Gotto (R-Nashville), said the definition is based on state criminal code. Sexual contact is the “intentional touching” of another person’s “intimate parts, or the intentional touching of the clothing covering the immediate area of ... any other person’s intimate parts, if that
intentional touching can be reasonably construed as being for the purpose of sexual arousal or gratification,” according to section code.

Rep. John DeBerry (D-Memphis) spoke out in favor of the bill. “Everyone in this room knows what gateway sexual activity is,” he said, noting that leaving teens without classroom guidance has resulted in the state caring for thousands of neglected or abused children.

SB 3310 calls for the family life curriculum taught in schools to have an “emphatic and exclusive” focus on abstinence; current law calls only for an emphasis on abstinence. The measure also allows parents to bring charges against an instructor for condoning “gateway sexual activity.”

Site Touts Safe Sex for Seniors

Asbury Park Press, (04.27.2012)
SaferSex4Seniors.org aims to give older Americans increased access to sexual information they may be too embarrassed to ask about. The website’s April debut coincided with National STD Awareness Month.

The site’s content focuses on heightening elders’ awareness about STDs, and it features a 31-second video encouraging safe sex. Melanie Davis, a certified sexuality educator and webmaster, said the concept came about through work with DDB NYC, the ad agency that created the video. It depicts fully clothed, older adult couples replicating sexual positions from the Kama Sutra, to the tune of original dance music, while a safe-sex message is displayed.

The interactive website offers viewers answers to frequently answered questions (FAQs) and allows them to submit questions for online response from experts, said Davis. Designed by Frank Stallone of Hoverboard Media, the website offers content authored by sexuality educators, trainers, and therapists, such as gynecologist Dr. Judith Hersh and sex therapist Melissa Donahue, who partner with Davis at the New Jersey Center for Sexual Wellness.

Topics covered include condoms and STDs, broaching sex conversations with one’s doctor, relationships, desire and pleasure, intimacy and cancer, gender identity and sexual orientation, and sexual rights in long-term-care settings.

Davis contends some facilities “will not allow partners to be together, be intimate, and have any privacy,” and said the FAQs include some “you should ask before putting a loved one or yourself into a situation.”

Testing the Fathers: Carrying Out HIV and STI Tests on Partners of Pregnant Women

Sexually Transmitted Infections Vol. 88; No. 3: P. 184-186, (04..2012)  R. Dhairyawan; S. Creighton; L. Sivvour; J. Anderson
In the current study, the authors present results from a pilot initiative to offer sexual health and HIV screening to the male partners of women undergoing antenatal ultrasound examination at Homerton Hospital in London. The team noted that while opt-out antenatal testing for HIV has “significantly reduced” mother-to-child transmission of the virus, the risk remains for seroconversion during pregnancy from undiagnosed HIV-positive partners.

Between Aug. 1, 2010, and Jan. 31, 2011, men whose female partners presented for routine ultrasound examination were offered onsite serology for HIV, syphilis, hepatitis B, and hepatitis C, as well as urine testing for Neisseria gonorrhoeae and Chlamydia trachomatis. The genitourinary medicine service provided follow-up results, and referral pathways were established for men whose results were positive.

A total of 1,243 male partners of 2,400 women attended the ultrasound exams. Of these, 430 men accepted testing, for an acceptance rate of 35 percent and a coverage rate of 18 percent. The men’s median age was 32 (range 19-52); 112 (26 percent) were of black ethnicity. A previous HIV test was reported by 41 percent. No difference in prior HIV testing was noted between whites and non-whites. No HIV diagnoses were made, but the testing diagnosed 16 others cases of infection: hepatitis C (two), hepatitis B (eight) and C. trachomatis (six).

“The authors have shown that it is acceptable and feasible to engage heterosexual men for testing in this setting,” the study concluded. “Of those men who accepted HIV testing, more than half had never been previously tested. Four percent of men tested had an infection, which had the potential to affect the outcome of the pregnancy.”
CNN Reports On China's 'One-Child Policy,' Implications For Women

CNN reports on how "[t]he issue of forced abortions – and in some cases, forced sterilizations – in China has seized the spotlight in recent days with news of escaped activist Chen Guangcheng," who "rose to fame in the late 1990s because of his advocacy for what he calls victims of abusive practices, such as forced abortions, by Chinese family planning officials." China's so-called "one-child policy has been blamed for abuses," the news service reports. The news service writes, "In some cases, advocates say, fetuses identified as female are aborted, ... abandoned, left to die or raised as orphans," as "Chinese traditionally prefer boys over girls." CNN describes several reports from women's health advocates working in China of women undergoing forced abortion and sterilization; a report from the Congressional-Executive Commission on China, "created by Congress to monitor human rights and the rule of law in China"; and the State Department's 2009 Human Rights Report, the news service notes.

"On a January 2011 visit to the United States, Chinese President Hu Jintao reportedly denied that China was forcing women to submit to abortions," CNN writes, adding, "Rep. Ileana Ros-Lehtinen (R-Fla.) who gave Hu a list of human rights concerns, said that Hu insisted a forced-abortion policy did not exist, according to media reports." And "[i]n November, according to state-run news agency Xinhua, Premier Wen Jiabao, in a speech to the National Working Conference on Women and Children, 'urged banning illegal fetus gender identification and illegal abortion,'" according to the news service. China has started a national campaign to reduce the rates of "non-medical sex determinations and sex-selective abortions to balance the gender ratio,' Xinhua said," according to CNN (Hayes/FlorCruz, 5/1)

'Taboo' Surrounding Toilets, Sanitation Hindering Progress Toward Improved Access

"Governments are failing to fund projects to improve access to toilets and other sanitation services in poor countries because the subject remains 'taboo,' a director at the Bill & Melinda Gates Foundation said on Monday," Reuters reports. "About 1.1 billion people across the world still defecate in the open because they have no toilets, according to the United Nations," Reuters writes. "It's the last big taboo and as a result more than one million kids die every year. Diarrhea is the second largest cause of death after respiratory infections in young children," Frank Rijsberman, director of water, sanitation and hygiene at the foundation, said at the Global Water Summit 2012 conference in Rome, the news service notes.

"Rijsberman said global leaders should take opportunities like the U.N. conference for sustainable development in Rio in June to set new sanitation targets," Reuters writes. "Governments are still far from meeting an internationally agreed Millennium Development Goal (MDG) for sanitation – only 63 percent of the world now has improved access to sanitation, well below the target of getting that to 75 percent by 2015," the news service notes, adding, "By contrast, the world has met the MDG to halve the proportion of people with no safe drinking water well ahead of the 2015 deadline, according to U.N. data released in March" (Hornby, 5/1).

Efforts To Fight Cholera In DRC Need To Include Sanitation, Waste Facility Improvements, Behavior Change, UNICEF Official Says

A cholera epidemic that began in January 2011 in the Democratic Republic of Congo (DRC) is continuing because of "poor hygiene, lack of awareness of the population about transmission mechanisms, very limited access to protected and monitored water sources and lack of sanitation infrastructure," according to Nona Zicherman, chief of emergency operations in DRC for UNICEF, IRIN reports. Since the beginning of the epidemic, more than 30,000 cholera cases have been identified and more than 700 people have died of the disease since June 2011, the news service states. Zicherman "noted that emergency and medium- and long-term interventions to limit the spread of cholera needed to be developed," including disinfecting contaminated areas, monitoring water sources, changing behaviors related to hygiene, and constructing water supply and sanitation facilities, according to IRIN (4/30).

'Mandatory Oversight' Of Potentially Dangerous Biological Research Will Be Necessary

"In the sobering annals of disaster prevention, genetic manipulation of the H5N1 influenza virus is looming as a seminal case," John Steinbruner, director of the Center for International Security Studies at the University of Maryland, writes in an opinion piece in The Hill's "Congress Blog," noting that two "laboratory experiments have rendered the highly virulent avian strain transmissible among ferrets, strongly suggesting that it would be transmissible among humans as well." He states, "If the virus could achieve efficient transmissibility while retaining anything like its current case fatality rate [of 50 percent],
it could inflict global disaster of unprecedented proportions." The actions of the U.S. National Science Advisory Board for Biosecurity, initially recommending publication of redacted versions of the two studies then reversing that decision, "implicitly concedes that the U.S. alone cannot exercise comprehensive jurisdiction," Steinbruner writes.

Though "some prudential oversight of highly consequential biological research is being practiced in some countries," it is "largely voluntary," inconsistent, and not global in scope, he states, adding, "A more effective arrangement would have to be mandatory and would have to be based on the principle of independent oversight applied to other matters of great consequence," such as economy or nuclear weapons. Steinbruner outlines his vision of the "basic features of an appropriate oversight arrangement" for biological research, including vetting by global public health experts, and notes "less than one percent of current biomedical research efforts would be affected." He concludes, "[I]t is prudent to assume that protective regulation will ultimately have to be imposed. Whether comprehension evolves naturally or is forced by disaster, mandatory oversight will eventually be indispensable. The sooner and the more gracefully that is realized the better off we all will be" (4/30).

**Preventing Mother-To-Child Transmission Of HIV Is 'Smart Investment'**
"Each year, nearly 400,000 children are born with HIV globally, and prevention of mother-to-child transmission (PMTCT) is a particular challenge in sub-Saharan Africa, an area characterized by weak health systems," U.S. Global AIDS Coordinator Ambassador Eric Goosby writes in the State Department "DipNote" blog. "Last year PEPFAR and UNAIDS joined with other partners to launch the Global Plan, an initiative to eliminate new HIV infections among children and keep their mothers alive," Goosby writes and reflects on a two-day mission to Nigeria with UNAIDS Executive Director Michel Sidibe last week. He concludes, "Preventing new HIV infections in children is a smart investment that saves lives, and the United States is proud to partner with Nigeria and other countries in this cause" (4/30).

**Large-scale analysis finds majority of clinical trials don't provide meaningful evidence**
DURHAM, N.C.—The largest comprehensive analysis of ClinicalTrials.gov finds that clinical trials are falling short of producing high-quality evidence needed to guide medical decision-making. The analysis, published today in JAMA, found the majority of clinical trials is small, and there are significant differences among methodical approaches, including randomizing, blinding and the use of data monitoring committees.

"Our analysis raises questions about the best methods for generating evidence, as well as the capacity of the clinical trials enterprise to supply sufficient amounts of high quality evidence to ensure confidence in guideline recommendations," said Robert Califf, M.D., first author of the paper, vice chancellor for clinical research at Duke University Medical Center, and director of the Duke Translational Medicine Institute.

The analysis was conducted by the Clinical Trials Transformation Initiative (CTTI), a public-private partnership founded by the Food and Drug Administration (FDA) and Duke. It extends the usability of the data in ClinicalTrials.gov for research by placing the data through September 27, 2010 into a database structured to facilitate aggregate analysis. This publically accessible database facilitates the assessment of the clinical trials enterprise in a more comprehensive manner than ever before and enables the identification of trends by study type.

The National Library of Medicine (NLM), a part of the National Institutes of Health, developed and manages ClinicalTrials.gov. This site maintains a registry of past, current, and planned clinical research studies.

"Since 2007, the Food and Drug Administration Amendment Act has required registration of clinical trials, and the expanded scope and rigor of trial registration policies internationally is producing more complete data from around the world," stated Deborah Zarin, MD, director, ClinicalTrials.gov, and assistant director for clinical research projects, NLM. "We have amassed over 120,000 registered clinical trials. This rich repository of data has a lot to say about the national and international research portfolio."

This CTTI project was a collaborative effort by informaticians, statisticians and project managers from NLM, FDA and Duke. CTTI comprises more than 60 member organizations with the goal of identifying practices that will improve the quality and efficiency of clinical trials.

"Since the ClinicalTrials.gov registry contains studies sponsored by multiple entities, including government, industry, foundations and universities, CTTI leaders recognized that it might be a valuable
source for benchmarking the state of the clinical trials enterprise," stated Judith Kramer, MD, executive director of CTTI.

The project goal was to produce an easily accessible database incorporating advances in informatics to permit a detailed characterization of the body of clinical research and facilitate analysis of groups of studies by therapeutic areas, by type of sponsor, by number of participants and by many other parameters.

"Analysis of the entire portfolio will enable the many entities in the clinical trials enterprise to examine their practices in comparison with others," says Califf. "For example, 96% of clinical trials have ≤1000 participants, and 62% have ≤ 100. While there are many excellent small clinical trials, these studies will not be able to inform patients, doctors and consumers about the choices they must make to prevent and treat disease."

The analysis showed heterogeneity in median trial size, with cardiovascular trials tending to be twice as large as those in oncology and trials in mental health falling in the middle. It also showed major differences in the use of randomization, blinding, and data monitoring committees, critical issues often used to judge the quality of evidence for medical decisions in clinical practice guidelines and systematic overviews.

"These results reinforce the importance of exploration, analysis and inspection of our clinical trials enterprise," said Rachel Behrman Sherman, MD, associate director for the Office of Medical Policy at the FDA’s Center for Drug Evaluation and Research. "Generation of this evidence will contribute to our understanding of the number of studies in different phases of research, the therapeutic areas, and ways we can improve data collection about clinical trials, eventually improving the quality of clinical trials."

An analysis-ready copy of the ClinicalTrials.gov database is now available at www.ctti-clinicaltrials.org. Specialists from numerous therapeutic areas are now scrutinizing the contents to better understand how the number and characteristics of clinical trials match the perceived needs of the research communities. This dataset will be useful for academic institutions and also for pharmaceutical and device companies to produce reports showing the completeness of their data entry compared to other institutions. Advocacy groups can chronicle the number and types of trials in their area of interest. Data quality is likely to improve as a function of the accountability fostered by this transparency.

The results of other projects conducted by CTTI can be found on the CTTI web site along with general information about the organization.

**Garlic Compound Fights Source of Food-Borne Illness Better Than Antibiotics**

ScienceDaily (May 1, 2012) — Researchers at Washington State University have found that a compound in garlic is 100 times more effective than two popular antibiotics at fighting the Campylobacter bacterium, one of the most common causes of intestinal illness.

Their work was published recently in the *Journal of Antimicrobial Chemotherapy.*

The discovery opens the door to new treatments for raw and processed meats and food preparation surfaces.

"This work is very exciting to me because it shows that this compound has the potential to reduce disease-causing bacteria in the environment and in our food supply," said Xiaonan Lu, a postdoctoral researcher and lead author of the paper.

"This is the first step in developing or thinking about new intervention strategies," said Michael Konkel, a co-author who has been researching *Campylobacter jejuni* for 25 years.

"Campylobacter is simply the most common bacterial cause of food-borne illness in the United States and probably the world," Konkel said. Some 2.4 million Americans are affected every year, according to the U.S. Centers for Disease Control and Prevention, with symptoms including diarrhea, cramping, abdominal pain and fever.

The bacteria also are responsible for triggering nearly one-third of the cases of a rare paralyzing disorder known as Guillain-Barré syndrome.

Most infections stem from eating raw or undercooked poultry or foods that have been cross-contaminated via surfaces or utensils used to prepare poultry.

Lu and his colleagues looked at the ability of the garlic-derived compound, diallyl sulfide, to kill the bacterium when it is protected by a slimy biofilm that makes it 1,000 times more resistant to antibiotics than the free floating bacterial cell. They found the compound can easily penetrate the protective biofilm and kill bacterial cells by combining with a sulfur-containing enzyme, subsequently changing the enzyme’s function and effectively shutting down cell metabolism.
The researchers found the diallyl sulfide was as effective as 100 times as much of the antibiotics erythromycin and ciprofloxacin and often would work in a fraction of the time.

Two previous works published last year by Lu and WSU colleagues in Applied and Environmental Microbiology and Analytical Chemistry found diallyl sulfide and other organosulfur compounds effectively kill important food-borne pathogens, such as Listeria monocytogenes and Escherichia coli O157:H7.

Konkel cautioned that the recent work is still at the basic stage, well removed from an actual application. While eating garlic is a generally healthy practice, it is unlikely to prevent Campylobacter-related food poisoning.

However, "diallyl sulfide may be useful in reducing the levels of the Campylobacter in the environment and to clean industrial food processing equipment, as the bacterium is found in a biofilm in both settings," he said.

"Diallyl sulfide could make many foods safer to eat," said Barbara Rasco, a co-author on all three recent papers and Lu's advisor for his doctorate in food science. "It can be used to clean food preparation surfaces and as a preservative in packaged foods like potato and pasta salads, coleslaw and deli meats."

"This would not only extend shelf life but it would also reduce the growth of potentially bad bacteria," she said.

Journal Reference:

Armpits, Belly Buttons and Chronic Wounds: The ABCs of Our Body Bacteria
ScienceDaily (Apr. 30, 2012) — Minutes after you were born, bacteria moved in. Since then, their populations have exploded, diversified and spread—on your skin and eyes and in your mouth and gut, not to mention other places. These bacterial cells now far outnumber your own cells.

Some bacteria on your skin can cause infections, like antibiotic-resistant infections known as MRSA (methicillin-resistant Staphylococcus aureus). Preventing such illnesses is the reason for those restroom signs about proper hand washing.

But most bacteria on your skin are harmless, and some are actually very helpful. They ward off more dangerous bacteria, aid wound healing and shelter us from certain skin infections. For instance, Staphylococcus epidermidis protects us by taking up space that a more harmful bacterium would otherwise occupy.

Understanding how and why bacteria colonize particular places on the body could point to ways of treating skin and other conditions.

Chronic Wounds and Bacteria
In the quest to better understand the skin’s bacterial communities, Elizabeth Grice studied bacteria on 20 different body parts during a research fellowship at the National Institutes of Health. She learned that certain types of skin-dwelling bacteria thrive in warm, moist places like armpits and between toes. Others prefer wide, dry expanses like the backside.

She also discovered that each person's collection of bacteria is unique—like fingerprints. But unlike your fingerprints, the bacterial communities can change depending on your diet, environment, health, age and many other factors.

Certain diseases, like diabetes, also affect the bacteria on your skin. A major complication of diabetes is sores, or ulcers, on the feet that never heal. Grice suspects that high blood sugar, which is known to change the skin's structure, likely encourages a specific subset of bacteria to grow. And, after various research studies on mice, Grice concluded that the altered bacterial communities on diabetic mice prevent cuts from healing normally. She now hopes to find a way to manipulate the bacteria on the feet of people with diabetes to help ulcers heal.

Belly Buttons and Armpits
A group of scientists in North Carolina is making some big discoveries about the bacteria in one small body part—the navel. Last year, the scientists launched the Belly Button Biodiversity project and now they are almost ready to publish their findings. A sneak preview: Swab samples from about 200 volunteers' belly buttons contained an astonishing variety of bacteria—nearly 4,000 different strains, many of which are completely new to scientists.

The researchers know that the real number is actually much higher because the technique they’re using can’t distinguish every strain of bacteria. For instance, if they used the technique to identify mammals, dogs and cats would be grouped in the same category.
The scientists expected that, in addition to each person's special collection of bacteria, there would be a few common strains living on everyone. To their surprise, they could not find a single strain of bacteria common to all the volunteers. The researchers aren't yet sure what to make of this discovery. The belly button project is part of a broader effort called Your Wild Life that's working to identify all the organisms on and in the human body as well as those in homes and neighborhoods. The project, which is based in North Carolina, is using crowd-sourcing techniques to collect samples from around the country. Current studies focus on bacteria, fungi and insects.

A future project will be "Armpit-pa-looza"—a study of the microbes in the armpits of humans and other primates. Bacteria in the armpit produce a distinctive odor that we recognize in ourselves and others near us. Many scientists believe that this odor can communicate not only who we are, but also if we have certain diseases. A better understanding of armpit bacteria could have a wide range of applications in health and hygiene.

**Sialyllactose in Viral Membrane Gangliosides Is a Novel Molecular Recognition Pattern for Mature Dendritic Cell Capture of HIV-1**

**Abstract**

HIV-1 is internalized into mature dendritic cells (mDCs) via an as yet undefined mechanism with subsequent transfer of stored, infectious virus to CD4+ T lymphocytes. Thus, HIV-1 subverts a DC antigen capture mechanism to promote viral spread. Here, we show that gangliosides in the HIV-1 membrane are the key molecules for mDC uptake. HIV-1 virus-like particles and liposomes mimicking the HIV-1 lipid composition were shown to use a common internalization pathway and the same trafficking route within mDCs. Hence, these results demonstrate that gangliosides can act as viral attachment factors, in addition to their well known function as cellular receptors for certain viruses. Furthermore, the sialyllactose molecule present in specific gangliosides was identified as the determinant moiety for mDC HIV-1 uptake. Thus, sialyllactose represents a novel molecular recognition pattern for mDC capture, and may be crucial both for antigen presentation leading to immunity against pathogens and for succumbing to subversion by HIV-1.

**Author Summary**

Antigen-presenting cells such as dendritic cells (DCs) are required to combat infections, but viruses including HIV have evolved strategies to evade their anti-viral activity. HIV can enter DCs via a non-infectious endocytic mechanism and trick them into passing infectious virus on to bystander CD4+ T cells. Immature DC (iDCs) are characterized by high endocytic activity and low T-cell activation potential. Interestingly, several groups have shown that DCs that have undergone “maturation” (mDCs), a process that occurs on contact with a presentable antigen, capture higher numbers of HIV-1 particles than iDCs when they are matured in the presence of lipopolysaccharide. mDCs move to the lymph nodes where they have more opportunity to interact with T cells than iDCs, and thus to pass on infectious virus. But the molecular mechanism underlying HIV-1 uptake by mDCs has until now been elusive. Here we show that gangliosides, basic components of the host cell's plasma membrane, have an important role in this process. Gangliosides are known to be incorporated into the viral envelope membrane during the process of viral particle budding and here we show that they serve as viral attachment factors: they are recognized and enable HIV-1 uptake by mDCs. Thus, in addition to the well-known function of gangliosides as host cell receptors that mediate virus (e.g., polyoma and SV40) attachment and transport from the plasma membrane to the ER, we now demonstrate that they can also act as determinants for capture by mDCs. Furthermore, we identify a moiety composed of sialyllactose on HIV-1 membrane gangliosides as the specific domain recognized by mDCs. We propose that this novel recognition moiety might be crucial for inducing immune responses, but also critical to disseminate HIV-1 and other ganglioside-containing viruses.

**Freezing Parkinson's in its Tracks**

Wednesday, May 2, 2012

TAU researcher developing therapy to halt symptoms in Parkinson's patients

Parkinson's disease, a disorder which affects movement and cognition, affects over a million Americans, including actor Michael J. Fox, who first brought it to the attention of many TV-watching Americans. It's characterized by a gradual loss of neurons that produce dopamine. Mutations in the gene known as DJ-1 lead to accelerated loss of dopaminergic neurons and result in the onset of Parkinson's symptoms at a young age.
The ability to modify the activity of DJ-1 could change the progress of the disease, says Dr. Nirit Lev, a researcher at Tel Aviv University’s Sackler Faculty of Medicine and a movement disorders specialist at Rabin Medical Center. Working in collaboration with Profs. Dani Offen and Eldad Melamed, Dr. Lev has now developed a peptide which mimics DJ-1’s normal function, thereby protecting dopamine-producing neurons. What’s more, the peptide can be easily delivered by daily injections or absorbed into the skin through an adhesive patch.

Based on a short protein derived from DJ-1 itself, the peptide has been shown to freeze neurodegeneration in its tracks, reducing problems with mobility and leading to greater protection of neurons and higher dopamine levels in the brain. Dr. Lev says that this method, which has been published in a number of journals including the Journal of Neural Transmission, could be developed as a preventative therapy.

Guarding dopamine levels
As we age, we naturally lose dopamine-producing neurons. Parkinson’s patients experience a rapid loss of these neurons from the onset of the disease, leading to much more drastic deficiencies in dopamine than the average person. Preserving dopamine-producing neurons can mean the difference between living life as a Parkinson’s patient or aging normally, says Dr. Lev.

The researchers set out to develop a therapy based on the protective effects of DJ-1, using a short peptide based on the healthy version of DJ-1 itself as a vehicle. “We attached the DJ-1-related peptide to another peptide that would allow it to enter the cells, and be carried to the brain,” explains Dr. Lev.

In pre-clinical trials, the treatment was tested on mice utilizing well-established toxic and genetic models for Parkinson’s disease. From both a behavioral and biochemical standpoint, the mice that received the peptide treatment showed remarkable improvement. Symptoms such as mobility dysfunctions were reduced significantly, and researchers noted the preservation of dopamine-producing neurons and higher dopamine levels in the brain.

Preliminary tests indicate that the peptide is a viable treatment option. Though many peptides have a short life span and degrade quickly, this peptide does not. Additionally, it provides a safe treatment option because peptides are organic to the body itself.

Filling an urgent need
According to Dr. Lev, this peptide could fill a gap in the treatment of Parkinson’s disease. "Current treatments are lacking because they can only address symptoms — there is nothing that can change or halt the disease," she says. "Until now, we have lacked tools for neuroprotection."

The researchers also note the potential for the peptides to be used preventatively. In some cases, Parkinson’s can be diagnosed before motor symptoms begin with the help of brain scans, explains Dr. Lev, and patients who have a genetic link to the disease might opt for early testing. A preventative therapy could help many potential Parkinson’s patients live a normal life.

Bird Flu Transmission in Mammals
After much ado, Nature publishes the first report of a bird flu virus adapted for transmission in ferrets.

By Ruth Williams | May 2, 2012

A long-anticipated paper detailing the creation of an artificial strain of H5N1 bird flu virus that, while less lethal, is capable of transmission in mammals has been published today (May 2) in Nature. The report reveals that a real-world conversion of H5N1 to a form that could cause a pandemic in humans is potentially only a few mutations away.

“[The study] has disproven the tenet held by some influenza virologists that this particular high-pathology avian flu could not adapt to transmission in mammals,” said Stan Lemon of the University of North Carolina, who was not involved in the research. "Now we know that that can happen it is a bit of a wake-up call.”

Some scientists had doubted the possibility that H5N1 bird flu could adapt to human transmission, Lemon explained, because “influenza viruses are primarily viruses of birds... and previous human epidemics or pandemics have always had an H3 or an H1 hemagglutinin”—the protein that recognizes receptors on the surfaces of cells and allows the virus to enter. “There’s never been an H5 hemagglutinin gene in a virus that has been rapidly and efficiently transmitted between mammals,” he said.

And it might not take much to convert the H5 protein, noted senior author Yoshihiro Kawaoka of the University of Wisconsin, Madison in an email to The Scientist. "Only a few mutations are needed to confer...
transmissibility [in mammals],” he said. “This will make it important to stockpile vaccine and antivirals and optimize pandemic preparedness measures.”

Of course, this publication is not the first time the scientific community has heard about these results. Indeed, Kawaoka’s study, along with a similar study led by Ron Fouchier at the Erasmus Medical Center in Rotterdam, the Netherlands (which is pending publication at Science), has been making headlines since late last year, when the National Science Advisory Board for Biosecurity (NSABB) made the unprecedented move of recommending that certain details be redacted prior to publication, for fear that they could be used for wrongdoing. But after further discussion, both the NSABB and the World Health Organization (WHO) decided that it was in the best interest of science to publish both papers in full.

The publication does lay to rest some questions regarding the details of the study, such as the fact that the engineered virus is not as lethal as the naturally existing strains of H5N1, which have killed about half of the people they have infected. This is because Kawaoka and colleagues paired mutant H5 proteins, which conferred transmissibility among the ferrets, with virus particles from a much less deadly H1N1 virus, creating what are known as reassortant viruses. “This approach enabled us to focus on the role of the H5N1 virus hemagglutinin without the complex background of the other genes,” explained Kawaoka.

Randomly mutating the H5 gene, the researchers found two mutations that, in combination, allowed the viruses to bind to the mammal-specific receptors in vitro. They then tested the reassortant viruses in vivo, by putting the viruses up ferrets’ noses and caging these infected ferrets next to non-infected ferrets, which contracted the virus in a matter of days. During the infections, two additional mutations arose in H5 that conferred improved growth and transmission of the virus. But thanks to the less virulent H1N1 components, no ferrets died.

Despite the fact that the researchers are working with a combination of viruses, the study does have real-world significance, said Kawaoka. “Many influenza genomes are capable of reassorting to generate hybrid viruses if they infect one host.”

The team’s findings could both inform the development of vaccines and aid in the monitoring of circulating viruses for signs that they are acquiring mutations conferring transmission between mammals. “If surveillance teams know which mutations are important,” Kawaoka said, “they can be alert for the emergence of viruses with pandemic potential.”

In their attempt to prepare for such deadly outbreaks, however, the researchers might have created an alternative worst-case scenario, argued Richard Ebright of Rutgers University, New Jersey. “The research has benefits in terms of expanding our fundamental understanding of influenza evolution and biology, and some potential practical applications in terms of surveillance and response, but these benefits do not match, much less outweigh, the risks,” he said, which include not just bioterrorism, but accidental escape of the virus or deliberate release by a disgruntled or disturbed lab worker. (Read more about Ebright’s thoughts on the risks of such research in last month’s feature, “Deliberating Over Danger.”)

“On the other hand, there is a very definite risk, and I think of greater magnitude, that this virus will evolve in nature,” said Lemon. “Four mutations is not a lot, [especially considering that] RNA viruses are highly mutable—the kinds of viruses that very readily adapt to new environments.... We need to be ready to observe that happening, predict it happening, and counteract it. From my own perspective, the risks of nature being a terrorist here are much greater than the risks of some misguided scientist.”


Comments

Edward R. Mikol Collapse

Unless they produced an antidote with this research, publishing the findings is folly.

 Calling Nature a “terrorist” -to deflect from the historically-common, malignant human project of mass-murder for ideological reasons—is cute, but irrelevant.

Use the investigations to solve the threat, and keep the intermediate work under wraps to prevent conscious terrorists (Nature is not consciously intent on producing this pandemic while many human agents would be) from benefiting from “pure” scientists who appear unable to appreciate the reality of human destructiveness.

edo_mcgowan

Assume a mild outbreak that can be confined to a single community and that community is highly quarantined. This is what was done with SARS in Toronto. But, forgotten by all were routes out of the quarantined areas, namely the sewers. Sewer plants, we must remember, are major aerosol generators; that is a documented fact. Thus some questions that warrant consideration here would include: 1) do sewer plants kill all organisms that enter them—the answer is that they actually do a fairly poor job and that also has been documented. 2) even before the raw sewage gets to a disinfection stage within the sewer plant, which is usually at the tail end of the process, it is subjected to high rates of aeration, hence aerosol generation. These issues need serious consideration and thus contingency plans.

Dr Edo McGowan, Medical Geo-hydrology
U.N. Adopts Resolution On Young People's Sexual And Reproductive Rights
This RH Reality Check post by the International Planned Parenthood Federation Western Hemisphere Region (IPPFWHR) examines a "resolution in support of young people's sexual and reproductive health and human rights" adopted recently by member states at the 45th Session of the United Nations Commission on Population and Development (CPD). According to the post, "[k]ey points of the final resolution include: The right of young people to decide on all matters related to their sexuality; Access to sexual and reproductive health services ... that respect confidentiality and do not discriminate; The right of youth to comprehensive sexuality education; Protection and promotion of young people's right to control their sexuality free from violence, discrimination and coercion" (5/3).

Mad Cow California: What Is Atypical BSE?
Posted: 05/ 3/2012 7:08 pm
The downer dairy cow recently found stricken with mad cow disease in California was infected with an "atypical" strain. Such cases are thought to arise spontaneously, a notion the USDA seized upon to explain how the disease could arise despite their regulations. If anything, that fact highlights the weaknesses in the current feed rules. If mad cow disease can arise out of nowhere, then it's even more important to close the loopholes and stop the feeding of cattle blood to calves and chicken manure to cows to prevent it from spreading. And what the USDA didn't mention about the atypical strain found in California is that there's evidence it's a more dangerous form of the disease

The California cow died of a particularly virulent form of mad cow disease known as BASE, bovine amyloidotic spongiform encephalopathy, also known as L-type atypical BSE. Typical BSE was first documented in the '80s in Britain. Afflicted cows often became twitchy and aggressive, giving rise to the "mad cow disease" moniker, as their brains degenerated into a characteristic Swiss cheese-like appearance. Hence the scientific name, BSE: bovine (cow) spongiform (sponge-like) encephalopathy (brain disease).

Then cats started dying. Max, someone's pet Siamese, was the first non-bovine victim of the disease. Infectious pet food was implicated as the cause of Max's death from a never-before-described feline spongiform encephalopathy.

Then young people started succumbing to a human spongiform encephalopathy called Creutzfeldt-Jakob disease, a relentlessly progressive and invariably fatal dementia, often involving weekly deterioration into blindness and seizures as their brains became riddled with holes. CJD appears sporadically in one in a million people, but typically strikes only the elderly. The new cases among teenagers were dubbed "variant" CJD, a disease now understood to be caused by consuming contaminated meat (or by getting a blood transfusion from someone who did).

Despite massive contamination of the food supply, no more than a few thousand people are expected to die, suggesting a robust transmission barrier between cows and humans when it comes to BSE. The same may not be true of the atypical forms of BSE found in California and in the last two mad cows in Texas and Alabama. Experimental models of human infection suggest that the type of mad cow disease discovered in the California case "is a more virulent BSE strain... in humans," with "higher transmissibility" and causing a swifter death.

Just as one in a million people sporadically get CJD, evidence suggests one in a million cattle get atypical BSE. The U.S. cattle population hovers around 100 million. Though there is evidence of these sporadic human cases of CJD may be associated with infected cows or sheep, case control studies tie CJD more closely to the consumption of pork. A study co-authored by D. Carleton Gajdusek, recipient of the Nobel Prize in Medicine for his research on these diseases, found that "consumption of pork as well as its processed products (e.g., ham, scrapple) may be considered as risk factors in the development of Creutzfeldt-Jakob disease."

Though pigs have been proven susceptible to a porcine spongiform encephalopathy, the National Pork Producers Council claims that no naturally occurring cases of "mad pig" disease have ever been discovered. The Consumers Union, publisher of Consumer Reports, however, has petitioned the federal government to reopen an investigation into a case in which a USDA veterinarian may have found a cluster of suspect pigs in upstate New York.

New research just found that unlike the British strain, the atypical forms of BSE found in the U.S. cause animals to have difficulties in standing up, so instead of mad cow disease, it's more of a downer cow disease. Since we continue to feed slaughterhouse waste and blood to pigs, this raises the question
whether any of the **hundreds of thousands** of downed pigs that arrive at slaughter plants every year in the U.S. may be infected.

It's ironic that this new case of mad cow disease was discovered in California where a law excluding downed animals from the food supply was recently **overturned** by the Supreme Court.

In 2008, an undercover **investigation** by The Humane Society of the United States of a dairy cow slaughter plant in California showing that downers were being dragged to slaughter for school lunch hamburgers prompted California to strengthen its laws to keep downer livestock out of the food supply. The meat industry, represented by the National Meat Association and the American Meat Institute, responded by successfully suing the state of California to keep meat from downed animals on people's plates on the grounds that only USDA had the authority to determine which animals should not be forced to the kill floor for humane or public health reasons.

Sick animals can lead to sick people. An unequivocal ban on the slaughter of any farm animal unable even to stand may reduce the public health risk of myriad threats from **anthrax** and **E. coli** to **swine flu** and **Salmonella**. Spongiform encephalopathies are a special case, though, as they are caused by infectious agents that cannot be eliminated by cooking, pasteurization, or the rendering process used to make pet food. In fact, infection can survive even **incineration** at temperatures hot enough to melt lead. It is therefore the meat industry's responsibility to prevent sick animals from entering the food chain in the first place, by instituting a "bright line" ban on the slaughter of all downed livestock. In the California case, the animal was killed before she could be slaughtered. Next time we might not be so lucky.

**Undoing HIV's 'Invisibility Cloak': Revelation of How Certain Compounds Adhere So Strongly to HIV's Coat Points to a Fresh Therapeutic Approach**

ScienceDaily (Feb. 10, 2012) — Drug researchers hunting for alternative ways to treat human immunodeficiency virus (HIV) infections may soon have a novel target—its camouflage coat. HIV hides inside a cloak unusually rich in a sugar called mannose, which it uses to slip past the immune system before infecting its host's cells. Recently, however, biochemists discovered a family of chemical compounds that stick strongly to mannose. Understanding how this mechanism works could reveal a way to make drugs adhere to and kill HIV. Yu Nakagawa and Yukishige Ito at the RIKEN Advanced Science Institute in Wako and their colleagues from several research institutes in Japan are leading the effort: they have mapped the binding site of the mannose-binding compound pradimicin A1.

Mannose-binding compounds are particularly attractive to drug researchers thanks to their double-action anti-HIV effect. By sticking to mannose in the virus's coat, pradimicin A first freezes HIV's molecular machinery for entering and infecting its host's healthy cells. The virus responds by reducing the mannose in its coat thereby revealing itself to the immune system, which can then attack.

Unraveling just how pradimicin A recognizes mannose, however, has proven surprisingly difficult. In solution, the two components stick together in variously sized small clusters, confounding conventional analytical techniques such as solution-based nuclear magnetic resonance (NMR) and x-ray crystallography. Nakagawa, Ito and their colleagues side-stepped the clumping problem by using solid-state NMR, which allowed them analyze the compounds as solids, rather than in solution.

The research team's approach involved inserting carbon-13, a chemical label, into particular parts of the pradimicin A structure. Carbon-13 boosts the NMR signal wherever it is inserted, so the team could 'walk' around the compound and detect where it interacts most strongly with mannose.

The results revealed that pradimicin A curls up to form a cavity, within which the mannose structure sits. "Our study highlights the benefit of solid-state NMR methodology to investigate this interaction," says Nakagawa. "Solid-state NMR is, at present, the only technique to analyze such a complicated system." Flagging the potential utility of the technique, Nakagawa adds that: "Our analytical strategy might be applicable to other systems that similarly suffer from aggregation in solution."
Meanwhile, solid-state NMR can offer even more in probing mannose-pradimicin A binding, Nakagawa says. Having determined how and where pradimicin A grabs mannose, the team's next step will be to use the technique to identify the specific molecular interactions that bind the pradimicin A to this potential Achilles' heel of HIV.

**Journal Reference:**
Yu Nakagawa, Takashi Doi, Yuichi Masuda, K. Takegoshi, Yasuhiro Igarashi, Yukishige Ito. *Mapping of the Primary Mannose Binding Site of Pradimicin A*. Journal of the American Chemical Society, 2011; 133 (43): 17485 DOI: [10.1021/ja207816h](http://dx.doi.org/10.1021/ja207816h)

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**Copenhagen Consensus Report Argues For Expanding Family Planning Programs In 'High-Fertility' Countries**

As part of a series of *Slate* articles highlighting issues being examined by the Copenhagen Consensus Center, Bjorn Lomborg, director of the center, examines the implications of population growth on development indicators. In a research paper released on Thursday "for Copenhagen Consensus 2012, Hans-Peter Kohler of the University of Pennsylvania looks at sub-Saharan African nations that, among high-fertility countries, make the dominant contribution to world population growth," he notes, adding, "'High-fertility' countries today account for about 38 percent of the 78 million people that are added annually to the world population, despite the fact that they are home to only 18 percent of the population."

"Family-planning programs that facilitate a decline in fertility and a reduction in population growth rate would seem to be potentially highly beneficial interventions that should be expanded," but "as Kohler outlines, this conclusion has been subject to a long-standing and sometimes heated debate, often questioning the very basic pillars of this deduction," Lomborg writes. "Kohler draws on recent estimates to find that expanding family-planning services to all women with unmet needs—215 million women—would require an ... annual expenditure of ... $6.7 billion," according to Lomborg. "The benefits are large," he continues, noting that Kohler found that subsequent reduced maternal and child mortality, increased female education, employment and earning, and improved economic growth "could result in benefits worth about $90 to $150" for every dollar spent. Lomborg concludes, "Kohler's analysis adds further weight to the argument that family planning programs are a good economic investment, especially in light of continued population growth in the world's worst-off countries" (5/3).

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**Bisexual Behavior Among Chinese Young Migrant Men Who Have Sex with Men: Implications for HIV Prevention and Intervention**

AIDS Care Vol. 24; No. 4: P. 451-458, (04.2012) Yan Guo; Xiaoming Li; Yan Song; Yingjie Liu

To assess bisexual behavior and associated sociodemographic and behavioral factors among young migrant Chinese men who have sex with men, data from 307 Beijing MSM were analyzed.

Twenty-seven percent of the MSM reported they also were concurrently involved in sexual behavior with women (MSMW). The HIV infection rate among MSMW was 8.4 percent compared to 4.9 percent among MSM-only. The syphilis infection rate was 10.8 percent among MSMW compared to 23.7 percent among MSM-only.

Several HIV risk behaviors among MSMW were similar to those of MSM-only, including unprotected anal sex, multiple sex partners, commercial sex involvement, and substance use. Compared with MSM-only, MSMW were less likely to have undergone HIV testing or to have taken part in HIV prevention activities, and they knew less about condom use and HIV/AIDS. In addition, MSMW reported a higher rate of unprotected sex with female stable partners (79.5 percent) than with male stable partners (59.5 percent).

"Results indicated that MSMW were at a very high risk for both HIV infection and transmission," the team concluded. "Intervention efforts are needed to target this subgroup of MSM and promote AIDS knowledge and HIV/STD testing among MSMW, and to reduce HIV transmission through MSM's bisexual behavior."

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**Mumbai High Court: Insisting on Condoms for Sex Can’t Be Grounds for Divorce**

*Xinhua News Agency*, (05.04.2012)

A wife's refusal to have sex with her husband without a condom does not constitute grounds for divorce, the High Court in Mumbai has ruled. In his divorce petition, Pradeep Bapat said his wife refused to have unprotected sex with him, saying she did not want to have children because the couple was not financially stable. A two-judge panel rejected his plea and said his other grounds for legal separation, that his wife...
lacked cooking and cleaning skills, could not be grounds for divorce. “She wanted to give the child a better life. It is a mutual decision, and a husband cannot insist,” Justice P.B. Majmudar said, according to the Times of India. Noting that “a woman is not a slave,” the court said couples should get to know each other before marrying, especially in cases of arranged marriages.

Cell Membrane Is Patterned Like a Patchwork Quilt

ScienceDaily (May 4, 2012) — As the interface between the cell and its environment, the cell membrane, which consists of fats and proteins, fulfills a variety of vital functions. Scientists at the Max Planck Institute of Biochemistry in Martinsried near Munich have performed the first comprehensive analysis of the molecular structure of this boundary layer, and revealed precisely how it is organised. In yeast cells, the entire membrane is made up of independent domains, each containing just one or a few protein types. If a protein is relocated to an inappropriate domain, it may even fail to function.

The study shows that the membrane is a kind of patchwork quilt and should help scientists to gain a better understanding of basic cellular processes.

The cell membrane must process numerous signals from the environment and the cell interior in order to initiate appropriate molecular responses to changing conditions. For example, if certain messenger substances bind to the membrane, this can trigger the growth or division of a cell. The cell membrane has long been the focus of scientific research. One aspect that has remained largely unexplained, however, is exactly how its various components organise themselves. According to an early model, the fats (lipids) and proteins anchored in the membrane are in constant flux and do not form fixed structures. That at least some are organised in bounded domains was only proven quite recently, and only for a small number of proteins.

Researchers working with Roland Wedlich-Söldner, a group leader at the Max Planck Institute of Biochemistry, have now carried out the first comprehensive analysis of the molecular structure of the cell membrane. They used advanced imaging technologies for the purpose, enabling them to obtain much sharper images of the cell membrane and the marked proteins within them than were previously available. They discovered that domain formation in the cell membrane is not the exception, but the rule. Each protein in the cell membrane is located in distinct areas that adopt a patch- or network-like structure. The entire cell membrane thus consists of domains—like a kind of molecular patchwork quilt.

"Some areas contain more than one type of protein," says Roland Wedlich-Söldner. "Even if these molecules fulfil entirely different functions, they generally have one thing in common: they are attached to a shared domain in the membrane by a similar or identical molecular anchor." In another experiment, the scientists succeeded in demonstrating the extent to which the protein function depends on this specific environment: they replaced the original anchor in some proteins with another molecular variant. The modified proteins then relocated to a “foreign” domain that matched the new anchor. However, they were no longer able to function correctly in their new surroundings.

How then do proteins find the appropriate domain and remain associated with it, despite being relatively mobile in the plane of the membrane? The researchers were able to show that the lipids in the cell membrane play a central role in this process. Different lipids prefer to accumulate around certain protein anchors. Therefore, areas arise that are particularly attractive to proteins with a similar type of anchor. This could explain how cell membranes self-organise—another previously unanswered question in biology. The highly ordered structure of the cell membrane could help scientists to gain a better understanding of its many functions. "One may assume that many processes only function efficiently thanks to the formation of domains in the cell membrane," says Wedlich-Söldner. "It is possible that the

The membrane of the yeast cell is divided into different domains (highlighted in colour), giving it the appearance of a molecular patchwork quilt. (Credit: MPI f. Biochemistry/Wedlich-Söldner)
cell exploits a principle that also applies in everyday life: a certain degree of order makes it much easier to get things done."

**Journal Reference:**

**New Technique Could Identify Drugs That Help Fight Broad Range of Viruses**

ScienceDaily (May 4, 2012) — Results of a new study demonstrate the feasibility of a novel strategy in drug discovery: screening large numbers of existing drugs—often already approved for other uses—to see which ones activate genes that boost natural immunity.

Using an automated, high-volume screening technique, researchers at Washington University School of Medicine in St. Louis have identified a cancer drug that enhances an important natural response to viral infection in human cells.

"Over many years of research, we have developed a good understanding of the human body's own mechanisms to fight viruses," says the study's first author Dhara Patel, PhD, a postdoctoral research scholar at Washington University. "Instead of targeting the virus itself, which most current antiviral drugs do, we have designed a strategy to look for chemical compounds that will enhance this innate antiviral system."

The results of the study, led by Michael J. Holtzman, MD, the Selma and Herman Seldin Professor of Medicine, appear May 4 in *PLoS ONE.*

Of the 2,240 compounds the researchers tested, 64 showed increased activity in the cells' interferon signaling pathway, an important player in the body's response to viruses. The 64 compounds included many different classes of drugs treating conditions as diverse as depression, high blood pressure and ulcers. But the one that stood out is idarubicin, a cancer drug commonly prescribed to treat leukemia, lymphoma and breast cancer. Even at low doses, idarubicin significantly ramps up the interferon signaling system.

In treating cancer, idarubicin stops cells from dividing by blocking a protein that unwinds DNA. As long as DNA remains tightly packed, it can't be copied. And if DNA can't be copied, a cell can't divide. Interestingly, though, the researchers showed that idarubicin's antiviral effects are totally unrelated to what makes it a good cancer drug.

"We tested other cancer drugs that work the same way as idarubicin but have very different structures," Patel says. "Although they act the same way that idarubicin does in cancer cells, they had no effect on the interferon system."

Like many cancer drugs, idarubicin has toxic side effects, so it is unlikely to ever be prescribed for patients fighting viral infections. But, its identification demonstrates that the new strategy works.

"While idarubicin is not something you would give to a patient who has the flu, we are continuing to screen more drugs," Patel says. "We're starting to find compounds from different drug classes that are not so toxic and that have similar properties in enhancing interferon signaling. We're still validating them, but we're very excited about what we're finding."

Traditionally, techniques for drug discovery involve trying to enhance or inhibit a very specific interaction. To treat a particular disease, scientists might try to disable a harmful protein, or replace a missing one, for example. But such approaches assume that altering a specific interaction of interest will result in the desired effect.

"I think our technique accepts the fact that we don't understand everything that's going on in the cell," Patel says. "Instead of looking at one particular interaction, we measure the downstream effects."

She compares it to driving a car and trying to make it go faster.

"Traditionally, we would pick a specific part—a part of the car that we think is responsible for speed—and then test compounds that alter the part in a way that we think will make the car go faster," she says. "With our approach, we don't assume we know what is responsible for speed. Instead, we take entire cars, treat them with many different compounds, and just see which ones go faster."

Patel says this screening technique is unusual because it can identify drugs that enhance the body's own immune response to a broad range of viruses, unlike a vaccine, which only protects against a specific virus.

The method has also shed light on how some compounds with known antiviral properties actually fight viruses. In addition to cancer drugs, antidepressants and blood pressure medications, the initial 64 drugs they identified with increased interferon activity included some known antiviral drugs.
"We already knew some of these compounds had antiviral properties, we just didn't know why," Patel says. "Now we're starting to find out how they actually work."

**Reference:**

**Bacteria Discovery Could Lead to Antibiotics Alternatives**

Scientists have discovered an Achilles heel within our cells that bacteria are able to exploit to cause and spread infection. The researchers say their findings could lead to the development of new anti-infective drugs as alternatives to antibiotics whose overuse has led to resistance.

University of Manchester researchers studied *Listeria*—a potentially deadly group of bacteria that cause listeriosis in humans when digested—and found they are able to spread infection by hitching a ride on a naturally occurring protein called calpain.

"Bacteria produce a number of chemicals that allow them to invade a host and to establish an infection," said lead researcher Dr David Brough, who is based in Manchester's Faculty of Life Sciences.

"The chemicals produced depend upon many factors, such as the species of bacteria, the type of host, and also whether the infection grows inside or outside a cell.

"We have investigated the growth of *Listeria*, a pathogenic bacterium that grows inside cells. An essential step for its growth, and thus the infection, is the bacteria's ability to move from within one compartment in a cell to another.

"We discovered that in order for this particular type of bacteria to move and to grow some of the host cells biology is exploited, a protein called calpain. Without calpain the bacteria cannot move within the cell and so do not grow.

"This discovery highlights the possibility of using drugs against these host proteins to block infections, potentially reducing the need to use antibiotics."

**Reference:**

**Anti-inflammatory Factors Fight Bugs**

A combination of antibiotics and the body's own defensive metabolites clears bacterial infections faster than antibiotics alone.

By Megan Scudellari | April 25, 2012

Specialized compounds that naturally reduce inflammation in mice also help clear bacterial infections. A combination of these inflammation-resolving factors and antibiotics lowers the antibiotic dose needed to clear *E. coli* and *Staphylococcus*, according to a new paper in *Nature*.

The finding suggests it would be possible to stimulate a person's own defenses to enhance the effects of antibiotics—a potentially valuable weapon in the fight against increasing rates of antibiotic resistance.

"This paper bridges two seemingly different and distant areas of research—antimicrobial resistance and the resolution of inflammation," said Alberto Mantovani, an immunologist at the University of Milan in Italy who was not involved in the research. "It's an unexpected perspective."

In the fight against antibiotic resistance, "a lot of efforts are focused on better, more effective antibiotics," said Nan Chiang, an assistant professor at Brigham and Women’s and first author on the paper. "But we hope to address that problem from a different angle by stimulating a body's own defenses" against pathogens, she said.

The resolution of an inflammatory response—after immune cells have gathered and responded to an injury—used to be considered a passive return to normal, as the immune cells dispersed in the absence of inflammatory stimulus. But in 2000, Charlie Serhan and colleagues at Brigham and Women's Hospital at Harvard Medical School identified a class of fatty acid metabolites, dubbed "resolvins," present in the...
tissues of mice that actively reduce inflammation, lowering the activity of pro-inflammatory cells while increasing the action of other cells that clear dead tissue. (For more, read our January feature, “Resolving Chronic Pain.”)

“Our general view of the resolution of inflammation has changed dramatically over the last few years,” said Mantovani. “Now we know resolution is an actively orchestrated process, which involves many different molecules.”

Recently, Serhan and Chiang decided to examine the role of resolvins and other specialized pro-resolving mediators (SPMs) in infection. In *E. coli*-infected mice, the researchers identified three SPMs: RvD5, RvD1, and PD1. Upon closer examination, they found that the three compounds heighten a mouse’s ability to fight infection, stimulating phagocytes to eat the invading *E. coli* and increasing survival time.

The researchers also looked at the effect of the SPMs in infected human white blood cells (WBCs). As in the mice, “we found they were able to stimulate WBCs to clear the bacteria,” said Chiang.

Given SPMs’ role in fighting infection, the team hypothesized that the compounds might improve antibiotic treatment by heightening a host’s antimicrobial response. They were right: administering SPMs and antibiotics together led to a faster resolution of the infection that either compound alone in infections of two types of bacteria, *E. coli* and *Staphylococcus aureus*. And the combination lowered the antibiotic dose needed to clear an infection.

“It proves the principle that you can treat the host to clear an infection,” said Chiang. Since humans, like mice, have natural SPMs, stimulating one’s own infection-resolving program could be a way to decrease the amounts of antibiotics needed in therapies, she said, thus decreasing the overall amount of antibiotics in use—often considered a cause of antibiotic resistance.

But Mantovani cautioned about the translational possibilities of the treatment from mice into humans. “It would be hard to think of a clinical trial in which you would actually use antibiotic treatment and add in one of these compounds,” he said, since it wouldn’t be safe to reduce the antibiotic dosage of a person who has an infection just to test the combination of antibiotic and SPMs.

Still, he added, the study is valuable because it makes one consider the resolution of inflammation in a different way—not just as the final clearing of an infection but an active process that could be used against pathogens. “We should think about resolution also as a strategy to deliver the final hit to bugs,” he said. N. Chiang, et al., “Infection regulates pro-resolving mediators that lower antibiotic requirements,” *Nature*, 484:524-8, 2012.

**Telomeres in Disease** *(long)*

Telomeres have been linked to numerous diseases over the years, but how exactly short telomeres cause diseases and how medicine can prevent telomere erosion are still up for debate.

**By Rodrigo Calado and Neal Young | May 1, 2012**

The ends of linear chromosomes have attracted serious scientific study—and Nobel Prizes—since the early 20th century. Called telomeres, these ends serve to protect the coding DNA of the genome. When a cell’s telomeres shorten to critical lengths, the cell senesces. Thus, telomeres dictate a cell’s life span—unless something goes wrong. Work over the past several decades has revealed an active, though limited, mechanism for the normal enzymatic repair of telomere loss in certain proliferative cells. Telomere lengthening in cancer cells, however, confers an abnormal proliferative ability.

In addition to cancer, telomeres have been found to be involved in numerous other diseases, including liver dysfunction and aplastic anemia, a condition in which the bone marrow does not produce a sufficient supply of new blood cells. Telomere repair and accelerated telomere attrition can be molecular causes of these diseases, and targeting these processes may lead to the development of novel therapies.

**Chromosome tails**

Telomeres consist of hexameric nucleotide sequences (TTAGGG in humans) that are repeated hundreds to thousands of times at each extremity of each chromosome. Telomeric DNA is coated by a group of proteins, collectively termed shelterin, which serves to protect telomere structure. Because DNA can only be synthesized in one direction, the RNA primers at the chromosome’s ends cannot be filled in, and thus a small amount of DNA is lost with every cell division—a loss that occurs in the telomeres. During normal aging of an animal or in cell culture, cells divide and telomeres shorten. As telomeric sequences do not contain genes, no important genetic information undergoes erosion during DNA replication. When telomeres become critically short, the cell becomes senescent—it ceases to divide—or undergoes apoptosis—it dies.
Inadequate telomere repair and accelerated telomere attrition can be molecular causes of disease, and targeting these processes may lead to the development of novel therapies.

Telomere attrition explains the “Hayflick limit,” the number of divisions a cell is capable of undergoing in tissue culture before the cell stops dividing. Telomere length is therefore a type of “mitotic clock,” a measure of a cell’s proliferative history. Under circumstances in which cell proliferation continues despite critically short telomeres (usually about a few hundred hexanucleotide repeats), the telomere’s protective function is lost. Subtelomeric genetic information can be lost, and more importantly, recombination between chromosomes occurs, leading to chromosome instability, aneuploidy, and possible transformation to a cancer phenotype.

Some proliferative cells can elongate telomeres enzymatically through the telomerase complex. Telomerase (TERT) is a reverse transcriptase that employs a small RNA molecule (TERC) as a template to extend telomeres in cells. In this way, telomerase counterbalances the effects of cell division and cellular genetic “aging,” preventing senescence, apoptosis, and genetic instability. Telomerase-dependent telomere repair occurs naturally in some cells, such as embryonic and adult stem cells and some cells of the immune system—cell types that divide regularly to support development, maintain tissues, and combat infections, respectively. Telomere maintenance is also possible by other mechanisms, such as the alternative pathway (ALT), which uses recombination between chromosomes to maintain telomere length. In ALT, telomeres are not newly elongated, but rather transferred from one chromosome to another, resulting in some daughter cells whose chromosomes have shorter telomeres and others with longer telomeres. The details of ALT’s components and regulation, however, are not well understood.

**Telomere Timeline**

In the 1930s, Hermann Muller and Barbara McClintock observed that fragmented chromosomes tended to fuse with each other, while normal chromosomes were stable, and they predicated characteristics of the “natural ends” to explain this difference. Muller named these ends “telomeres.”

Almost 40 years later, Alexey Olovnikov, on theoretical grounds, and James Watson, based on phage experiments, recognized a fundamental problem regarding the mechanics of DNA replication, during which a small amount of genetic information is lost with every cell division. In the late 1970s, Elizabeth Blackburn and Joseph Gall discovered the structure of telomeres—short, highly repetitive noncoding nucleotide sequences—in the ciliated protozoan *Tetrahymena*. In 1982, Blackburn and Jack Szostak elucidated how telomeres in yeast could serve as a buffer for the coding DNA during replication, and postulated the existence of an enzyme that could rebuild telomeres—an enzyme discovered by Blackburn and Carol Greider in *Tetrahymena* 3 years later. By 1988, the sequence of the human telomere was known, and researchers began actively investigating its role in aging and cancer. Subsequent work showed that the telomeres in certain proliferative cells are actively repaired. For their work on telomeres, Blackburn, Greider, and Szostak were awarded the 2009 Nobel Prize in Physiology or Medicine.

**Telomere shortening and cancer**

Most cells in which telomeres reach critically short lengths either die or enter senescence. In those few that survive, perhaps due to inadequate monitoring by p53 and related DNA damage-response safeguards, telomere repair would be subject to powerful selective pressure. Indeed, in most malignancies, telomerase gene upregulation or activation of the ALT pathway is thought to be necessary for the establishment of cellular immortality. Telomerase is so frequently increased in tumors and in cancer cell lines as to be considered an appropriate therapeutic target. Currently there are several clinical trials using telomerase inhibitors to treat a variety of cancers, but results have yet to be reported. Telomere shortening would also generate the equivalent of a “mutator phenotype” by increasing spontaneous chromosomal aberrations—from numerical changes to structural abnormalities—and would therefore increase the pool of aberrant cells upon which selection would act.
There are many sources of evidence suggesting that telomere attrition is associated with and likely etiologic of cancer. Patients with dyskeratosis congenita, a rare inherited bone marrow failure disease characterized by telomerase dysfunction, have a 1,000-fold increase in risk of tongue cancer and about a 100-fold increase in risk of acute myeloid leukemia. In aplastic anemia, patients with the shortest telomeres (absent mutations) are 4- to 5-fold more likely to have their disease undergo malignant transformation to myelodysplasia and leukemia. Telomere-free ends of chromosomes and aneuploidy may be apparent in cultured bone marrow years before progression to leukemia. Furthermore, some acute myeloid leukemia patients without prior bone marrow failure have inherited mutations in TERT and TERC.

Similarly, short leukocyte telomeres predict the development of cancer in patients with Barrett’s esophagitis, a condition in which the lining of the esophagus is damaged by stomach acid, or ulcerative colitis, a type of inflammatory bowel disease. In these diseases, the mechanism is less clear. Short telomeres in blood leukocytes may reflect the telomere length of the affected organ. Alternatively, they may be a biomarker of exposure to reactive oxygen species produced as a result of a chronic inflammatory process, which can both damage telomeres and cause cancer. Evidence for the latter hypothesis comes from the observation that cells cultured in room air have excessive telomere shortening in comparison to cells cultured at low oxygen tension.

More generally, genome-wide analyses have identified single nucleotide polymorphisms in TERT as risk factors in many cancers. In a recent report, short leukocyte telomeres were associated with increased risk of all cancers and of cancer fatalities in a large population followed over a decade. Circumstantially, telomere attrition is an accompaniment of aging, itself a major risk factor for cancer. Furthermore, secondary malignancies often occur after chemotherapy and radiation, which would be anticipated to cause marrow stress and telomere shortening. More direct data come from animal experiments. In a knockout mouse model, animals with reduced telomerase activity combined with diminished p53 surveillance of DNA damage developed a variety of epidermal cancers unusual in the rodent but typical of humans.

**Telomeres and Cancer**

When telomeres reach critically short lengths, most cells either stop dividing or die. In many cancers, however, telomerase is upregulated or the ALT pathway is activated, resulting in abnormal telomere lengthening and proliferative growth. Because of this link between telomeres and cancer, researchers are actively investigating telomerase (TERT) as a target for cancer therapeutics, with several clinical trials ongoing.

**Evidence for a telomere-cancer link:**

- Genome-wide analyses have identified single nucleotide polymorphisms in the TERT gene as risk factors in many cancers.
- Some acute myeloid leukemia patients have inherited mutations in TERT and TERC, the RNA template used to extend telomeres.
- Short leukocyte telomeres have been associated with increased risk of all cancers and of cancer fatalities.
- Shortened telomeres and aneuploidy may be apparent in cultured bone marrow years before progression to leukemia.
- Among aplastic anemia patients, whose bone marrow does not produce sufficient new blood cells, those with the shortest telomeres are 4- to 5-fold more likely to have their disease undergo malignant transformation to...
myelodyplasia and leukemia.

- Patients with dyskeratosis congenita, an inherited bone marrow failure disease characterized by telomerase dysfunction, have a 1000-fold risk of tongue cancer and about 100-fold risk of acute myeloid leukemia.
- Knockout mice with reduced telomerase activity combined with diminished p53 surveillance of DNA damage develop a variety of epidermal cancers.

Other telomere diseases

In addition to cancer, other diseases have been linked to telomeres. Hematopoietic stem cells express telomerase in response to the enormous daily demand for red blood cells, white blood cells, and platelets. Thus while overexpression of telomerase in other tissues can cause malignant growth, faulty telomere repair in blood stem cells can also result in severe diseases caused by stem cell failure.

One such “telomere disease” is dyskeratosis congenita, an X-linked bone marrow disorder characterized by symptoms such as abnormal nails, a pigmented, net-like rash, a white patch or plaque in the mouth, and aplastic anemia. The disease usually presents in the first decade of life. The liver and lungs can also be affected, as is often observed after a hematopoietic stem-cell transplant is performed to correct the bone marrow disease. The reasons for liver and lung involvement are not clear, but the chemotherapy used for transplant conditioning and the new inflammatory cells in the transplanted bone marrow may accelerate the injury in these organs.

Patients suffering from dyskeratosis congenita inherit a mutation in a gene named \( DKC1 \), identified by Inderjeet Dokal at the Hammersmith Hospital in London, who performed linkage studies of large pedigrees. \( DKC1 \) encodes dyskerin, a protein that binds to the RNA component of the telomerase complex and stabilizes it. Later, heterozygous mutations in \( TERC \) were also found in some families with dyskeratosis congenita. The severe phenotype of X-linked dyskeratosis congenita is likely due to the loss of functional \( DKC1 \) and markedly reduced telomerase function, which results in defective telomere repair and leads to accelerated telomere attrition, causing cell senescence and organ failure.

Whereas dyskeratosis congenita caused by mutations in the \( DKC1 \) gene usually presents during infancy, mutations in \( TERC \) and in the enzymatic component encoded by \( TERT \) appear to have impacts later in life. The first \( TERT \) mutations found in humans were in adult patients with acquired aplastic anemia who lacked physical anomalies and did not have a family history of telomere-related disease. Penetrance of the phenotypes of \( TERT \) and \( TERC \) mutations is highly variable among and within families, as reflected by the severity, time of onset, and organs involved. Within pedigrees, members with the identical mutation may have minimal or no clinical manifestations, develop aplastic anemia late in life, or suffer pulmonary fibrosis (scarring of the lungs) or hepatic cirrhosis (scarring of liver tissue). Different organ systems may be affected in different family members at different times, and occasional patients have disease in marrow, lung, and liver. How faulty telomere repair leads to such diseases is not fully understood.

Even with the uncertainties that remain, the association of telomerase mutations with disease in such disparate organs systems has important practical consequences for patients and their physicians. In the family history, the presence of even mild blood count abnormalities, pulmonary fibrosis, and hepatic cirrhosis, as well as acute myeloid leukemia, are important clues for the diagnosis of a telomeropathy. Involvement of multiple medical subspecialties can be confusing: some patients have even made their own diagnoses after Internet searches. Telomere length in leukocytes can be measured commercially and is a reliable marker of these diseases when severely reduced. Sequencing \( TERT \) and \( TERC \) can also be diagnostic. The appropriate finding of a telomerase deficit has consequences for prognosis, treatment, and genetic counseling. But while the diagnosis of telomeropathies can be straightforward, there may be complications. Some typical families lack known mutations, and telomere length may be normal even in the presence of etiologic nucleotide substitutions. Furthermore, rare mutations in shelterin genes coding for the proteins that protect telomere structure can produce severe dyskeratosis but do not alter telomerase repair capacity. And regulatory regions of genes, not routinely screened, may be responsible in some cases.

Telomeres and aging

Telomeres shorten as we age. By analogy to the cellular mitotic clock, telomeres have been postulated as a marker of “genetic age,” and telomere length has been marketed as a simple predictor of longevity. Assays of telomere length have been bundled with recommendations for lifestyle modification and for drug therapy, neither based on appropriate clinical studies. Simple but appealing arguments relating telomeres and aging are currently controversial, likely simplistic, and potentially harmful. Telomere length does indeed reflect a cell’s past proliferative history and future propensity for apoptosis, senescence, and transformation. Cellular aging, however, is not equivalent to organ or organismal aging.
There are several considerations in relating telomere biology to aging. First, physiologically there is overlap between the shortest telomere length of young children and the longest telomeres of the elderly. Most telomere shortening occurs early in life, in association with growth, and when the rate of disease in general is low. The paradigmatic telomere syndrome of dyskeratosis congenita is not at all typical of progerias, inherited syndromes in which patients appear old and suffer diseases of aging such as premature atherosclerosis or dementia. Furthermore, the organ damage of dyskeratosis congenita is not very similar to normal aging of marrow, lungs, and liver. The marrow becomes mildly hypocellular in older individuals, but stem cell numbers may actually increase, and blood counts remain stable; and neither the liver nor lungs normally become fibrotic with advanced age, as they often do in dyskeratosis congenita patients. Although in adults, relatively short leukocyte telomeres have been associated with cardiovascular events—a common morbidity of the aging population—the clinical correlations have not been consistent, and may be related to overall reactive oxygen species exposure.

Studies in humans have attempted to relate telomere length to life span. In the provocative initial publication from the University of Utah in 2003, individuals around 60 years of age who had the longest telomeres lived longer than did subjects with the shortest telomeres, but the main cause of death in the latter group was, inexplicably, infectious disease; the persons with shorter telomeres did not have a higher rate of cancer deaths. Moreover, these findings have not been confirmed in other studies of older subjects. In another study evaluating a different population, telomere length failed to predict survival, but interestingly it correlated with years of healthy life. In a Danish study of people aged 73 to 101 years, telomeres correlated with life expectancy in a simple univariate analysis, but only before the researchers corrected for age, suggesting that the correlation was driven simply by the fact that younger subjects had longer telomeres. And a Dutch study of 78-year-old men found that while telomere lengths eroded with age, they failed to correlate with mortality. These discrepancies may have several causes. In some analyses, telomere lengths may have been studied as a surrogate marker of age. In addition, retrospective studies may identify “positive” associations that are random and cannot be reproduced in follow-up investigations.

The telomere hypothesis of aging also has been modeled in mice. For instance, in a murine model of telomerase deficiency and accelerated telomere attrition, researchers found that certain intracellular pathways involved in mitochondrial function and glucose metabolism were deregulated, a common occurrence in aging individuals, ultimately causing heart muscle disease. Interestingly, telomerase reactivation in these mice restored glucose production and heart function. However, these abnormalities observed in telomerase-deficient animals were not those typical of humans with very short telomeres; patients with telomeropathies usually do not suffer from heart disease. Indeed, the translation of mouse experiments on telomeres to human physiology and disease should be done with caution. Mice are not the ideal model for telomere attrition and its effects on aging as murine telomeres are 5 to 10 times longer than human telomeres, in spite of mice having a much shorter life span. When telomerase is knocked out in mice, they live a healthy life for several generations, and even late-generation animals with very short telomeres do not display the clinical phenotypes characteristic of human telomeropathies. Telomerase-deficient mice also do not have a higher incidence of cancer, which happens only if the p53 gene also is modulated, in contrast to humans with telomerase deficiency, who are at very high risk of developing cancer.

**Implications for medicine**

Telomeres and their repair are important in the growing field of regenerative medicine. Dolly the sheep had chromosomes with shorter telomeres probably because she was cloned from an adult mammary gland cell. This may have contributed to Dolly’s illnesses, especially her progressive lung disease. Embryonic stem cells, however, express telomerase and are able to maintain their telomere lengths despite numerous cell divisions. More recently, reprogramming mature adult skin cells to the pluripotent state has been achieved with introduction of just a few defined nuclear factors. During the process of reprogramming cells to a more immature and pluripotent state, the reprogrammed cells’ telomeres are highly elongated. In the first steps of reprogramming and likely in the early stages of embryogenesis, cells can elongate, and thus “rejuvenate,” their telomeres. Since telomere shortening limits cell proliferation, mechanisms that can elongate telomeres are highly desirable for effective regenerative medicine.

Telomerase expression is tightly regulated in the cell; just a few copies of the complex are present in the cell nucleus, and they exert their function during certain specific periods of the cell cycle. The mechanisms that modulate telomerase gene expression, resultant enzymatic activity, and telomere elongation are the focus of intensive research. MYC, a proto-oncogene that regulates the expression of many genes and cell pluripotency, activates telomerase expression. Sex hormones also activate telomerase...
expression in reproductive and nonreproductive organs, such as the bone marrow. The promoter region of the telomerase gene contains regulatory sequences that are modulated by estrogen; cells exposed to estrogens (or androgens converted into estrogens) upregulate telomerase expression. In retrospect, the clinical response of improved blood cell counts in patients with aplastic anemia, especially children with inherited marrow failure, to androgens may be attributable to this mechanism. However, whether higher blood levels of sex hormones or exposure to exogenous sex hormones causes telomere elongation is still unknown.

Conclusions
Telomeres and telomere repair are basic molecular processes in cells possessing linear DNA chromosomes. Accelerated telomere attrition due to genetic defects in telomerase and in the shelterin protein genes is etiologic in several human diseases not previously considered related in the clinic. These include aplastic anemia, pulmonary fibrosis, and hepatic cirrhosis. The telomeropathies, especially in their milder and more chronic forms, may not be rare and almost certainly are often unrecognized by physicians. The importance of telomere repair in tissues under regenerative stress is of special interest, particularly in the reactive responses of fibrogenesis in the liver and the lungs. The maintenance of adequate telomere lengths also may be important in embryonic and adult stem cells to enable proliferation while preventing chromosome instability, thus avoiding potential malignant transformation. Also of interest is the connection linking telomere attrition and chronic inflammation to cancer and other diseases. (See “An Aspirin for Your Cancer,” The Scientist, April 2011.)

There is still much to be learned about how telomerase gene mutations cause disease, why they only affect certain organs, and how telomeres can be targeted for therapies. Both the genetic regulation of telomerase expression and the effect of an organism’s environment on telomere attrition are poorly understood. Drugs or hormones that might modulate telomerase expression and maintain or elongate telomeres would be appealing in the treatment of the telomeropathies and in conditions in which telomere attrition has known medical consequences. Whether telomere shortening mediates human aging—and conversely, whether telomere elongation may reverse aging or prevent age-related diseases—are still controversial issues.

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References

Data Diving
What lies untapped beneath the surface of published clinical trial analyses could rock the world of independent review.
By Kerry Grens | May 1, 2012
A few weeks before Christmas 2009, the world was in the grip of a flu pandemic. More than 10,000 people had died, and roughly half a million people had been hospitalized worldwide; tens of millions had been infected. In the United States, millions of doses of Tamiflu, an antiviral medication, had been released from national stockpiles. December 2009 was a point in the H1N1 outbreak where there was a lot of talk
about a second or third wave of this virus coming back and being more deadly,” says Peter Doshi, now a postdoctoral researcher at Johns Hopkins University and a member of an independent team of researchers tasked with analyzing Tamiflu clinical trials. “Anxiety and concern were really peaking.”

So it was no small blow when, that same month, Doshi and his colleagues released their assessment of Tamiflu showing that there was not enough evidence to merit a claim that the drug reduced the complications of influenza. Their report had been commissioned by the Cochrane Collaboration, which publishes independent reviews on health-care issues to aid providers, patients, and policy makers. The findings, published in the British Medical Journal, made headlines around the world.

Doshi’s group arrived at this conclusion because they’d run into a lack of available data. Some of the widespread belief that Tamiflu could blunt pneumonia and other dangerous health consequences of flu was based on a meta-analysis of several clinical trials whose results had never been published. Because the data could not stand up to independent scrutiny by the researchers, these trials were tossed out of the Cochrane review; other published trials were disqualified because of possible bias or lack of information.

Just as the 2009 BMJ paper was to be published, Roche, the maker of Tamiflu, opted to do something unorthodox—the company agreed to hand over full clinical study reports of 10 trials, eight of which had not been published, so that independent researchers could do a proper analysis. Within a few weeks after the publication of its review, the Cochrane team was downloading thousands of pages of study files.

One publication of a Tamiflu trial was seven pages long. The corresponding clinical study report was 8,545 pages.

Clinical study reports are massive compilations of trial documents used by regulators to make approval decisions. Doshi says he had never heard of, let alone worked with, a clinical study report. “This is how in the dark most researchers are on the forms of data there are. Most people think if you want to know what happened in a trial, you look in the New England Journal of Medicine or JAMA.”

And in fact, that is how many meta-analyses or systematic reviews of drugs are done. As publications amass, independent analysts gather up the results and publish their own findings. At times they might include unpublished results offered by the trial investigators, from the US Food and Drug Administration’s website, or from conference abstracts or other “grey literature,” but for the most part, they rely simply on publications in peer-reviewed journals. Such reviews are valuable to clinicians and health agencies for recommending treatment. But as several recent studies illustrate, they can be grossly limited and misleading.

Doshi and his colleagues began poring over the reams of information from Roche, and realized that not only had their own previous reviews of Tamiflu relied on an extremely condensed fraction of the information, but that what was missing was actually important. For instance, they found that there was no standard definition of pneumonia, says Tom Jefferson of the Cochrane Collaboration and lead author of the 2009 review. And among people who had been infected with influenza, it appeared that the placebo and treatment groups were not on equal footing. “We realized that all of these [analyses] led to misleading results because the treatment groups [were] not comparable for that subpopulation,” Doshi says.

In January of this year, the group published its latest review of Tamiflu, which included the unpublished evidence obtained from Roche in 2009. The authors concluded that Tamiflu falls short of claims—not just that it ameliorates flu complications, but also that the drug reduces the transmission of influenza. In an e-mail sent to The Scientist, Roche says the Cochrane review was not limited to people who had laboratory-confirmed flu, but encompassed people with influenza-like symptoms, thereby possibly underestimating Tamiflu’s efficacy. “Independent and eminent scientists reviewed data from the Tamiflu trials, the inception and design of the studies which produced the data, and the assumptions made,” the company states. “Roche stands behind the robustness and integrity of our data supporting the efficacy and safety of Tamiflu.”

Jefferson is not convinced, and the experience has made him rethink his approach to systematic review, the Cochrane method of evaluating drugs. For 20 years, he has relied on medical journals for evidence, but now he’s aware of an entire world of data that never sees the light of publication. “I have an evidence crisis,” he says. “I’m not sure what to make of what I see in journals.” He offers an example: one publication of a Tamiflu trial was seven pages long. The corresponding clinical study report was 8,545 pages.

“It just blows the mind,” says Doshi. “A trial’s an extraordinarily complex process, and what we see in the published literature is an extreme synthesis of what goes on.” The big question is: What does that mean for the validity of independent reviews?
Unpublished data—Is it all bad news?

Clinical study reports like those provided by Roche are the most comprehensive descriptions of trials’ methodology and results, says Doshi. They include details that might not make it into a published paper, such as the composition of the placebo used, the original protocol and any deviations from it, and descriptions of all the measures that were collected.

But even clinical study reports include some level of synthesis. At the finest level of resolution are the raw, unabridged, patient-level data. Getting access to either set of results, outside of being trial sponsors or drug regulators, is a rarity. Robert Gibbons, the director of the Center for Health Statistics at the University of Chicago, had never seen a reanalysis of raw data by an independent team until a few years ago, when he himself was staring at the full results from Eli Lilly’s clinical trials of the blockbuster antidepressant Prozac.

FDA, time, Gibbons had questioned the belief that antidepressants are linked to an increased risk of suicide. Previous meta-analyses by independent reviewers on suicidal thoughts and behaviors among people taking the drugs had for the most part relied on summary data, Gibbons says. At a meeting at the Institute of Medicine a few years ago, Gibbons spoke with a senior investigator at Eli Lilly and brought up the idea of doing a full workup of the original data.

If there is some lid put on some aspects of those trials, that is frustrating one important goal of research, which is sharing information.

—Sidney Wolfe, Public Citizen

Much to his surprise, shortly after the meeting Gibbons was in possession of the numbers. “We haven’t seen anybody get these kinds of data,” he says. He decided to push his luck. Gibbons had served as an expert witness for Wyeth, and he approached attorneys for the pharmaceutical company to ask if they would also share data from trials of the company’s antidepressant Effexor. “They got back to me, and they were agreeable to provide all their adult data,” he recalls.

Gibbons and his colleagues went to work reanalyzing the data. “Everything was exquisitely well documented,” he says. The raw data allowed them to take into account each person’s depression severity and to determine individual outcomes rather than averages. Their results, published earlier this year, ended up bucking much of the published literature on antidepressants. For one, they found no link between Prozac and suicide risk among children and young adults. And secondly, they found that Prozac appeared to be more effective in youth, and antidepressants far less efficacious in the elderly, than previously thought. “I think these kinds of analyses and the discrepancies in the findings are good reason to be concerned about our reliance on traditional meta-analyses,” Gibbons says.

Although some of his results reflect negatively on the drugs, others are clearly very positive. There’s been an understanding for some time that publication bias is a real occurrence, and that it often favors the drug. Trials that show no efficacy are less likely to get into print than trials that demonstrate a positive effect. So when Lisa Bero at the University of California, San Francisco, decided to redo 42 published meta-analyses of drugs and include unpublished, but available, data, she suspected the drugs would fare poorly. “But that’s not what we found,” she says.

She and her colleagues analyzed nine drugs using unpublished data from the FDA. For any approved drug, the agency makes available a summary of data used to vet the medication. When Bero’s group added these data to the meta-analyses, they found that all but three turned out to have a different result.

Nineteen of the redone analyses showed a drug to be more efficacious, while 19 found a drug to be less efficacious. The one harm analysis that was reanalyzed showed more harm from the drug than had been reported. “We showed data that make a difference are not being published,” Bero says.

While the FDA’s summaries of trial data are available to any researcher, they’re not necessarily easy to work with, and often researchers don’t include them in meta-analyses. “I think the FDA reports are an extremely valuable data source, but they’re not the full application [for drug approval], and they have redacted parts,” Bero says. She’s found that potentially important elements, such as patient characteristics or conflict-of-interest information, have been blacked out. The quality of the PDFs can also be poor, with crooked pages or light print; and sometimes there is no index for a document hundreds of pages long.

Such data files are quite different from the quality of the documents Gibbons was able to work with. While he urges independent researchers to try to access raw data, he notes that “getting all the data is not a trivial problem.”

Why aren’t the data shared?

Although summaries of clinical trials are available from the FDA, unabridged clinical study reports or the raw data are hard to come by. Keri McGrath Happe, the communications manager at Lilly Bio-Medicines, wrote in an e-mail to The Scientist that the company has a committee that reviews requests to obtain
unpublished clinical trial results. “I can tell you that it is not common” to have a request filled for raw data, she says. “Granting access to raw data isn’t as easy as opening file cabinets and handing over documents. A team has to go through each piece of data to find what specific data [are] needed to fulfill the request.”

If being an administrative burden, handing over clinical reports or raw data is considered hazardous to the integrity of a drug’s worth. “The simple truth is that drug discovery is enormously expensive,” says Jeff Francer, the assistant general counsel of the Pharmaceutical Research and Manufacturers of America (PhRMA). “In order for companies to engage in the immensely capital-intensive work to develop a medicine, there has to be some protection of the intellectual property. And the intellectual property is the trial data.”

The FDA tends to concur. The agency receives much more information about a drug than it ever releases. According to Patricia El-Hinnawy, an FDA public affairs officer, “as a matter of law and regulation, patient-level clinical trial data has been historically regarded as confidential commercial and/or trade secret information.”

The other route to obtaining unpublished results is through a Freedom of Information Act (FOIA) request, but just as with putting in a request to a company, there is no guarantee that the information will be released. Plus, “FOIA requests take a long time,” says Michelle Mello, a professor of law and public health at the Harvard School of Public Health. “In a world where we’re concerned about being able to rapidly assess certain safety signals, this is not a route to producing timely information.”

Gibbons says his studies on antidepressants make a strong case for greater data sharing. The other argument, says Sidney Wolfe, director of the health research group at the advocacy organization Public Citizen, is that “it’s a moral and ethical thing too. People who are participating in clinical trials, aside from whatever possible benefit will happen to them . . . are doing it for the benefit of humanity. And if there is some lid put on some aspects of those trials, that is frustrating one important goal of research, which is sharing information.”

The question of whether results from human experiments are private information or a public good has been debated for some time. In 2010, the European Medicines Agency (EMA), the European Union’s equivalent of the FDA, finally made a decision. “We had resolved that clinical data is not commercial confidential,” says Hans-Georg Eichler, the EMA’s senior medical officer. “It doesn’t belong to a company, it belongs to the patient who was in the trial.”

Efforts to increase data sharing
The EMA’s new policy is that if someone requests data from clinical trials of an approved medication, the agency will provide it. Doshi’s group took advantage of this to obtain about 25,000 pages of information on Tamiflu, which they used for their 2012 Cochrane update.2

Eichler says there have only been a handful of requests to date, too few to know how the policy is working out. Fulfilling such requests can be cumbersome, he says. It takes time to carefully review the data and make sure patients cannot be identified. Eichler adds that in the future he’d like to see a system where all clinical trial results are entered into a system accessible by other researchers.

Under the FDA Amendments Act of 2007, the agency requires trial sponsors to post the summary results of registered trials on clinicaltrials.gov within one year of completing the trial. But few comply. A recent survey of the website found that of 738 trials that should have fallen within the mandate, just 163 had reported their results.2 In a statement sent to The Scientist, Congressman Henry Waxman (D-CA) says, “I was alarmed by the recent studies showing that compliance with this law has been sorely lacking and that industry is not reporting the required study results.”

While companies are certainly part of the problem in this case, they were actually more likely to report results than were researchers whose clinical trials had no industry backing, but were funded by foundation or government money. “I think it’s so important to acknowledge that is a huge problem throughout” the clinical research enterprise, says Kenneth Getz, a professor at Tufts Center for the Study of Drug Development. And industry has made some moves to be more proactive about sharing data.

Last year, the medical device company Medtronic agreed to share all of its original data regarding Infuse, a bone growth product that had been facing considerable skepticism about its efficacy. Yale professor Harlan Krumholz approached the company with a challenge: if Medtronic thinks the Infuse data can stand up to external scrutiny, then let an external group have a look. The company agreed, and a Yale University group serves as the middleman between the company and the independent reviewers.

Joseph Ross, a Yale Medical School professor who’s involved in the project, says two review teams have been selected, and they should have results by the summer. Medtronic is paying $2.5 million for the external reviews, a price Ross says is small compared to what gets invested in—and ultimately earned.
from—a successful drug. He says it’s the first experiment of its kind. “In my most optimistic moments I think it has to be the way of the future. I don’t think the public realized that this data isn’t available for everybody to understand,” says Ross. “In my most pessimistic moments, this only happens one other time—when a company gets in hot water.”

Journals are also lighting a fire under trial sponsors to provide their results to independent reviewers more quickly and completely. In 2005, the International Committee of Medical Journal Editors initiated a requirement that trials had to be registered, say on clinicaltrials.gov, in order to be published. “That sent shock waves,” says Elizabeth Loder, an editor at the British Medical Journal.

Since then, Loder’s own publication has been digging into the effects of unpublished data. She says the BMJ asks independent reviewers and meta-analysts to what extent they tried to obtain unpublished results for their studies. And this January, the journal published a special issue of reports dedicated to “missing” clinical trial data. “I suppose you could say that publishing the original [2009] report on Tamiflu, we were newly sensitized to the dangers,” says Loder. “I think we wanted to keep everybody focused on that problem.”

For a special issue next year, Loder says BMJ is going to look at what exactly is the harm of having used incomplete data sets for so many meta-analyses and systematic reviews over the years. “Even though going forward new requirements for posting study results will probably improve the situation, we remain concerned about previously done studies that are unpublished and unavaiable, and how that might affect the existing evidence base.”

While Getz agrees that more data could improve meta-analyses, he cautions against “data dumping”—completely opening the floodgates to unpublished results. “I think just the idea of making more information available misses the point. You reach a level of data overload that makes it very hard to draw meaningful and reasonable conclusions, unless you’re an expert with a lot of time.”

But Cochrane Collaboration’s Jefferson says bring it on. While the clinical study reports he received numbered in the thousands of pages, they were still incomplete. Roche says it provided as much as the researchers needed to answer their study questions. But accepting that response would require a trust that is clearly eroded. “We hold in the region of 30,000 pages. That’s not a lot,” Jefferson says. “We don’t know what the total is. We’re looking at the tip of the iceberg and we don’t know what’s below the waterline.”

References

FDA Panel Considers HIV Drug for New Use
Wall Street Journal, (05.06.2012) Jennifer Corbett Dooren
On Thursday, a Food and Drug Administration advisory panel will consider whether to recommend that FDA approve the first drug for high-risk but healthy people to take to prevent HIV infection. Truvada, made by Gilead Sciences Inc., is already one of the most widely used drugs to treat HIV infection. Gilead has submitted data from two large clinical trials to support marketing Truvada as pre-exposure prophylaxis (PrEP).

Gilead submitted one study involving about 2,500 at-risk gay and bisexual men that found the drug, in addition to other prevention measures like condom use, reduced their HIV infection risk by 44 percent. In another involving about 4,800 serodiscordant heterosexual couples, HIV infection risk was cut 73 percent among HIV-negative partners taking Truvada, interim data showed. But a study among some 2,000 women was stopped last year after it was determined it was unlikely to show whether Truvada helped prevent infection among them.
The AIDS Healthcare Foundation filed a petition in March urging FDA to reject the application, saying PrEP data are not strong enough. AHF also cited worries over side-effects, the drug’s $14,000-a-year cost, and adherence problems. However, the prevention advocacy group AVAC is among 14 organizations calling for FDA's approval.

Dr. Rodney Wright, AHF’s board chair, said he is concerned about “a blanket approval” of Truvada for PrEP and the lack of data for it among women. Wright and other physicians already prescribe Truvada as PrEP on a limited basis, including for serodiscordant couples wishing to have children. CDC last year released interim PrEP guidelines for certain men who have sex with men, and it is weighing similar guidance for heterosexuals.

"PrEP will be the most beneficial for people at very high risk of HIV infection,” but strict adherence to the daily regimen is essential, said Jonathan Mermin, director of CDC’s Division of HIV/AIDS Prevention.

**Cholera Strain In Haiti Evolving, CDC Reports**
"The cholera strain in Haiti is evolving, researchers reported Thursday, a sign that it may be taking deeper root in the nation less than two years after it appeared and killed thousands of people," the Associated Press/USA Today reports. "The study released by the U.S. Centers for Disease Control and Prevention indicates that the bacterium is changing as survivors acquire at least some immunity to the original bug, which apparently was imported from Nepal," the news service writes (Daniel, 5/5). "The evolution of the cholera strain was expected and typical of the disease, according to the CDC," CBS Miami notes (5/4).

"This suggests that the ongoing epidemic in Haiti might be entering its next phase, since we see these shifts where cholera is endemic,' said Dr. Edward T. Ryan, an infectious disease specialist with Massachusetts General Hospital who was not involved with the study," the AP writes, adding, "The change also means it could be easier for Haitians to fall ill a second time to the new cholera version because they don't have full immunity to it if they don't take precautions such as washing their hands or chlorinating water." The news service notes that "[i]n an effort to stem the spread of the disease, the Boston-based Partners in Health and its partner, the GHESKIO Center, have launched a campaign to vaccinate 100,000 Haitians, or one percent of the national population, in a neighborhood in Port-au-Prince and in a rural area north of the capital" (5/5).

**Scientific American Examines Worldwide Spread Of Drug-Resistant Gonorrhea**
Scientific American examines how strains of cephalosporin-resistant gonorrhea have "been emerging in Japan, and moving east and west from there, for at least a decade." The magazine writes, "Rapid international travel allowed the resistance mutation to hopscotch the globe," noting antibiotic-resistant strains that have been identified in Sweden, England, Norway, the Philippines, Spain, and France. "'We can't go back to older antibiotics,' says Peter Leone, who is board chair of the National Coalition of STD Directors and medical director of North Carolina's STD prevention program. 'Once resistance emerges in gonorrhea, it is there for good. Cephalosporins are all we have left,'" he added, according to Scientific American. The magazine writes that efforts "to educate physicians and patients, to track resistant strains and to develop new treatments ... must be carefully targeted and well coordinated with one another," and concludes, "If not, truly untreatable gonorrhea, and its expensive, destructive consequences, could be the worldwide result" (McKenna, 5/4).

**Man-Made Waterways Contribute To Malaria Breeding Grounds, Study Suggests**
A recent study, conducted by Elizabeth Whitcombe, visiting senior research scholar at the earth system science interdisciplinary center at the University of Maryland, and published in the May 13 issue of Philosophical Transactions of the Royal Society, "mapped meteorological, irrigation and medical reports during British rule in India" and concluded modern-day India should learn lessons from the past to improve engineering plans and epidemiological "modeling of environmental factors controlling vector borne disease," especially malaria, SciDev.Net reports. "Ashvin Kumar Gosain, professor at the department of civil engineering, Indian Institute of Technology, Delhi, however, disagreed that scientists were ignoring the link between irrigation and disease," according to the news service. "Studies are being done even now and the linkage between river flows and disease is being studied once again in the context of climate change," he said, SciDev.Net reports (Sreelata, 5/4).
Oral zinc may lessen common cold symptoms but adverse effects are common
Oral zinc treatments may shorten the duration of symptoms of the common cold in adults, although adverse effects are common, according to a study published in *CMAJ (Canadian Medical Association Journal)*.

Canadian researchers looked at 17 randomized controlled trials with 2121 participants between 1 and 65 years of age to determine the efficacy and safety of zinc in treating the common cold. All trials were double-blinded and used placebos as well as oral zinc preparations. The authors found that, compared with placebos, zinc significantly reduced the duration of cold symptoms, although the quality of evidence was moderate. High doses of ionic zinc were more effective than lower doses at shortening the duration of cold symptoms.

"We found that orally administered zinc shortened the duration of cold symptoms," writes Dr. Michelle Science, The Hospital for Sick Children (SickKids), Toronto, with coauthors at McMaster University. "These findings, however, are tempered by significant heterogeneity and quality of evidence."

There was weak evidence that people taking zinc were less likely to have symptoms after one week, although there was no difference in symptoms between the two groups at three days. While zinc appeared to reduce the duration of symptoms in adults, there was no apparent effect in children. Participants taking zinc treatment were more likely to experience adverse effects including bad taste and nausea.

Previous studies have shown conflicting effects of zinc in reducing cold symptom severity and the duration of symptoms.

"Until further evidence becomes available, there is only a weak rationale for physicians to recommend zinc for the treatment of the common cold," conclude the authors. "The questionable benefits must be balanced against the potential adverse effects."

Gut flora affects maturation of B cells in infants
Infants whose gut is colonised by *E. coli* bacteria early in life have a higher number of memory B cells in their blood, reveals a study of infants carried out at the Sahlgrenska Academy at the University of Gothenburg, Sweden.

The bacteria in our gut outnumber the cells in our bodies by a factor of ten and are extremely important for our health because they stimulate the maturation of the immune system. The normal bacterial flora in the gut is established at the very beginning of our lives, but an increasingly hygienic lifestyle has led to changes in this flora.

Colonised ever later
These days Swedish children are colonised by *E. coli* bacteria later and later. They also have a less varied bacterial flora and a smaller turnover of bacterial strains in the gut than children in developing countries. Meanwhile, diseases caused by deficiencies in immune regulation have increased sharply, making allergies a major public health issue in the Western World.

B cells play key role in development of allergies
Researchers at the University of Gothenburg's Sahlgrenska Academy have looked at B cells, a type of white blood cell that produces antibodies that can protect the body against infection and play a key role in the development of allergies. By studying 65 healthy newborn babies in the Västra Götaland region, researcher Anna-Carin Lundell and her colleagues were able to show that infants whose gut is colonised by *E. coli* bacteria during the first few weeks of life had a higher number of memory B cells at the age of both four and 18 months.

"The results are important for understanding the relationship between our complex bacterial gut flora and our immune system, and show what we risk losing with an excessively hygienic lifestyle," Anna-Carin Lundell explains.

"Most of the bacteria around us are harmless, and we should see them as a very important form of training so that our children's immune systems mature properly. Healthy newborns should not be over-protected against natural exposure of the gut flora."

The article "Infant B cell memory differentiation and early gut bacterial colonization" is soon to be published in the *Journal of Immunology*. I may 2012

Cuba’s Fortresses Against a Viral Foe
José Goitia for The New York Times
Santiago de las Vegas, the first sanitarium for H.I.V. patients to open in Cuba, still has 200 patients. It is on the grounds of Los Cocos, an estate that belonged to a relative of an ousted dictator.
By DONALD G. McNEIL Jr.

SANTIAGO DE LAS VEGAS, Cuba — When H.I.V. testing began in Cuba in 1986, infections were found first in soldiers who had been in Africa. Initially locked in the national Naval Hospital, they were frustrated, since they were still healthy. There were escapes on bedsheet ropes; rum was smuggled in.

As their numbers grew and more civilians tested positive, the government opened sanitariums — both to keep the infected from having sex with anyone uninfected and to help them die comfortably. At first the institutions were run by military doctors and guarded by soldiers; patients had home visits only with escorts.

But life inside was not brutal. Inmates got food, medical care and their old salaries; theater troupes and art classes formed. Gay men could live together, which was not true in the macho culture outside.

The network of sanitariums grew to 14. They were harshly criticized — Dr. Jonathan Mann, the first AIDS director at the World Health Organization, called them “pretty prisons” — but they had a huge damping effect on the early epidemic. Fewer than 150 new cases were detected in the country each year through 1990.

The policy had a few unintended consequences. To stay out, some Cubans tried to avoid testing. But a few others, usually teenagers estranged from their families, deliberately got themselves infected to get in.

The policy also affected the virus; researchers believe Cuba’s 11 unique recombinant H.I.V. strains emerged from intra-sanitarium sex.

Starting in 1989, a new director of the network, Dr. Jorge Pérez Ávila, who is now Cuba’s leading AIDS physician, slowly eased restrictions. Trusted patients could leave without escorts.

In 1993, the gates were opened and outpatient care became the norm. Initially, however, 40 percent of the inhabitants stayed. With the Soviet Union’s collapse, “those were really bad days,” Dr. Pérez said. “The economy was destroyed.”

Now, however, just three sanitariums remain. A reporter was allowed to visit two.

Santiago de las Vegas, the first to open, still has 200 patients, down from 340 at its peak. It is about a half-hour drive southwest of Havana, on the grounds of Los Cocos, an estate that belonged to a relative of the ousted dictator Fulgencio Batista. (The large oil of a flamenco dancer in the hacienda, according to snickering but unverifiable sanitarium lore, was the former owner in drag.)

Some of its buildings are rundown, but it is still lush, with fountains, lawns and towering palms. Patients like Carlos Emilio García, a nurse who also works inside, live rent-free in white bungalows with TVs, air-conditioning, refrigerators and stoves. In the psychiatric ward, five patients watched TV under the eyes of two nurses.

The sanitarium in Sancti Spíritus, in central Cuba, is more disheveled but is being spruced up. A former vacation camp for the Ministry of Construction, it has 63 employees. But the patient population is down to 21.

NYTimes, May 7, 2012

A Regime’s Tight Grip on AIDS (long)

By DONALD G. McNEIL Jr.

HAVANA — Yudelsy García O’Connor, the first baby known to have been born with H.I.V. in Cuba, is not merely still alive. She is vibrant, funny and, at age 25, recently divorced but hoping to remarry and have children.

Her father died of AIDS when she was 10, her mother when she was 23. She was near death herself in her youth.

“I’m not afraid of death,” she said. “I know it could knock on my door. It comes for everyone. But I take my medicine.”

Ms. García is alive thanks partly to lucky genes, and partly to the intensity with which Cuba has attacked its AIDS epidemic. Whatever debate may linger about the government’s harsh early tactics — until 1993, everyone who tested positive for H.I.V. was forced into quarantine — there is no question that they succeeded.

Cuba now has one of the world’s smallest epidemics, a mere 14,038 cases. Its infection rate is 0.1 percent, on par with Finland, Singapore and Kazakhstan. That is one-sixth the rate of the United States, one-twentieth of nearby Haiti.

The population of Cuba is only slightly larger than that of New York City. In the three decades of the global AIDS epidemic, 78,763 New Yorkers have died of AIDS. Only 2,364 Cubans have.
Other elements have contributed to Cuba’s success: It has free universal basic health care; it has stunningly high rates of H.I.V. testing; it saturates its population with free condoms, concentrating on high-risk groups like prostitutes; it gives its teenagers graphic safe-sex education; it rigorously traces the sexual contacts of each person who tests positive.

By contrast, the response in the United States — which records 50,000 new infections every year — seems feeble. Millions of poor people never see a doctor. Testing is voluntary, and many patients do not return for their results. Sex education is so politicized that many schools teach nothing about protected sex; condoms are expensive, and distribution of free ones is haphazard.

Cuba has succeeded even though it has the most genetically diverse epidemic outside Africa. Almost all American cases are of one strain, subtype B. Cuba has 21 different strains.

The genetic diversity is a legacy of its foreign aid. Since the 1960s, Cuba has sent abroad thousands of “internationalists” — soldiers, doctors, teachers and engineers. Stationed all over Africa, they brought back a wide array of strains. According to a study in 2002, 11 of Cuba’s 21 strains are unknown elsewhere, formed when two others mixed.

And Cuba’s success has come despite its being a sex tourism destination for Europeans and Canadians.

While the police enforce laws against overt streetwalking, bars and hotel lobbies in downtown Havana are filled with young women known as jineteras — slang for “jockeys” — who approach foreigners, asking if they would like to go for a drink, or perhaps dancing, with the unspoken assumption that it will lead to more. Even so, of the roughly 1,000 new infections diagnosed each year, 81 percent are among men and very few among young unmarried women.

“Most of those who sleep with tourists know to use condoms,” said Dr. Ribero Wong, an AIDS specialist here.

In a survey in 2009, 77 percent of all sex workers said they regularly used condoms.

There are male jineteras for gay tourists too, of course, “but we believe the main vector is within the people,” said Dr. Luis Estruch Rancán, deputy minister for public health. “Mainly, the very promiscuous group in the homosexual community who have many partners and don’t take precautions.”

One example is Carlos Emilio García, 50, a registered nurse who lives and works at a former quarantine sanitarium outside Havana. He had negative H.I.V. tests at his job every six months from 1990 to 1996, but became infected in 1997.

He admits to having had many partners; as he put it, “No, I don’t know who my assassin is.”

Asked why a well-educated nurse would risk sex without a condom, he waved his hands in the air and replied, “You know — because we all do crazy things sometimes.”

The few Cuban women who are infected usually get the virus from partners who are secretly bisexual, experts said.

“Homo-bisexual transmission” is its own category in Cuba; socially, a man who occasionally has sex with other men is not considered gay if he is a “top” — the penetrative partner, explained Ramón Arango García, a fashion designer and educator at the National AIDS and Sexually Transmitted Disease Prevention Center.

Heroin use, which drives epidemics in many countries, is virtually nonexistent in Cuba, officials insist.

And since 1986, only 38 babies have been born with the virus. In Cuba’s cradle-to-grave health care system, pregnant women get up to 12 free prenatal checkups, during which they are tested for H.I.V. at least twice.

Before antiretroviral drugs were available, H.I.V.-infected women were offered abortions or, if they chose to deliver, Caesareans and free infant formula to discourage breast-feeding and reduce the risk of transmission. Now they get the drugs free.

Universal Coverage

As broken as it is economically, Cuba still points proudly to one legacy of its 1959 revolution: Basic health care is universal and free. Cuba has 535,000 health care workers (“We’re all either doctors or baseball players,” one hospital microbiologist joked) and each citizen is officially registered with a family doctor nearby; if a patient skips a checkup, the doctor is expected to find out why.

“I was trained to expect my patients to come to me,” said Dr. Rafael Mázín, senior AIDS adviser for the Pan American Health Organization in Washington, who is Mexican. “In Cuba, the doctor comes to you.”

Cuba is tied with the United States in both life expectancy and infant mortality.

Dr. Jorge Pérez Ávila is Cuba’s Tony Fauci, its best-known AIDS doctor. He is grandfatherly now, and clearly much loved by former patients like Ms. García, but he has memories of helping his bus driver
father make gasoline bombs to throw at the police during the Batista government. As a teenager he dropped out of school to live in the mountains, teaching villagers to read under a literacy program after Castro came to power.

He treated Ms. García’s parents on their deathbeds and heard her father beg, “Do whatever it takes to help my daughter live.” (Her father, who had been a soldier in Angola, was a truck driver. He had nine girlfriends in different towns, five of whom he infected.)

Many medical authorities agree that Cuba had an early and effective response to the epidemic. In his book, “AIDS: Confessions to a Doctor,” published only in Spanish, Dr. Pérez gave his account of the meeting that galvanized Cuba’s response.

In 1983, Fidel Castro visited the Pedro Kourí Institute, Cuba’s top tropical disease hospital, to hear a presentation on malaria and dengue fever.

As it ended, he suddenly asked the director, “Gustavo, what are you doing to keep AIDS from entering Cuba?”

Dr. Gustavo Kourí, son of the institute’s founder, was caught off guard, Dr. Pérez said, and stammered: “AIDS, comandante? AIDS? It is a new disease. We don’t even know whether it’s produced by a bacteria, a virus or a fungus. There isn’t much data on it, just what’s been reported in the United States and a few cases in Europe. It will take time to know how big it is.”

Mr. Castro replied: “I think it will be the epidemic of this century. And it’s your responsibility, Gustavo, to stop it becoming a major problem here.”

This was two years before any American president publicly uttered the word “AIDS.” Asked how Mr. Castro could have been so prescient, Dr. Pérez struggled to find the right word, then said: “Castro has luz larga” — “big lights,” the Cuban slang for automobile high beams. “He reads a lot. He sees far ahead.”

Dr. Pérez is simultaneously both a fan of the Castro government and a bit of a cynic; on Dec. 1, he led a “Viva, Fidel!” cheer at his hospital’s World AIDS Day.

But he also mentioned that Mr. Castro once praised him by saying: “Jorge, I’ve been reading your mail. Your patients say very nice things about you.”

The medical establishment reacted quickly. The first step was to throw out all imported blood — 20,000 units. That avoided the devastation that the hemophiliac populations in the United States and France suffered.

Doctors were sent to Brazil and France to study cases. All of the country’s family doctors were ordered to watch for infections that indicate AIDS like Kaposi’s sarcoma or Pneumocystis carinii pneumonia.

Because there was no H.I.V. test yet, the first cases were found late in the disease, leading doctors to think most patients died within a year — an erroneous assumption that helped justify the quarantine policy.

In 1986, blocked by the embargo from buying American test kits, Cuba bought 750,000 French ones.

According to Dr. María Isela Lantero, AIDS chief at the Health Ministry’s, Cuba’s 11 million citizens have been tested 43 million times; last year, more than two million tests were done. That is the equivalent of testing the sexually active population every three years, though in reality the focus is on high-risk groups, who are tested more often.

Cubans returning from abroad are routinely tested, as are pregnant women, prisoners, soldiers, hospital patients, health workers and anyone treated for venereal disease. So is anyone whose family doctor suspects he or she is gay, a sex worker or otherwise at risk.

Haydee Martínez Obregón, 33, who has lived in the AIDS sanitarium in Sancti Spíritus, in central Cuba, since she was 19, is an example of that. (She lives there by choice, she said, because she has no home outside.)

Asked how she learned she was infected, she said, “My family doctor thought it was a good idea to test me because I was so promiscuous.”

And how did he know that?

“My mother told him everything.”

Anonymous voluntary testing is also available at 700 clinics and hospitals. Anyone who tests positive gets an appointment with an epidemiology nurse, who asks for the names of everyone he or she has ever slept with.

By law, answering is voluntary.

“If they say no, nothing happens,” Dr. Pérez said.

But pressure is clearly applied. A patient who says no to the nurse gets an appointment with the doctor, then with a social worker and then sometimes with a psychologist. Then a team of H.I.V.-positive educators will make a home visit. So might the local Committee for the Defense of the Revolution.
Depending on whom one asks, those committees are the defenders of Cuban democracy, domestic spies or just state-sponsored Nosy Parkers.

Some still refuse. Araceli Castro, a professor of global health at Harvard Medical School who often works in Cuba, described one woman who absolutely insisted that she had never slept with anyone but her husband, who was virus-free.

“We called her the Immaculate Infection,” she said.

There are other subtle pressures, Dr. Castro said. Socialist education teaches Cubans to feel responsible for one another. Also, most Cubans subsist partly on government rations and the sick get extra food, and their lifesaving drugs, from the government.

Everyone who tests positive also must take a two-week course in “living responsibly with H.I.V.”

**Rising Challenge**

With mandatory quarantine long gone and the virus now mostly in gay and bisexual men, new infections are slowly but steadily rising. They now approach 1,000 a year, “and we’re waiting for the plateau,” said Dr. José Joanes Fiol, the Health Ministry’s chief epidemiologist.

Today, condoms and sex education are the chief weapons.

Cuban society is the opposite of puritanical; scanty clothing is routine, suggestive flirtation is common, and so are divorce and extramarital affairs.

The government distributes more than 100 million condoms a year. Every place with young customers, even pizzerias, is required to stock them.

“The first ones we got were from China, and had butterflies and penguins on the package,” Manuel Hernández Fernández, an AIDS educator for 25 years, said with a snort. “We had to Cubanize them.”

Now one shows a man groping a naked breast; another has two men.

During a condom giveaway for World AIDS Day, women laughed as volunteers — mostly gay men — dropped condoms into their cleavages.

“Just one?” one woman said. “What am I going to do with just one?”

Omairy Lorenzo, 18, a journalism student in Havana watching the giveaway, said she had been shown how to put a condom on a model penis at school when she was 12.

Her classmate Abel Lescaille, 20, said, “Sometimes they do so much sex education that you get tired of it.”

Until recently, Cuban society and government policies were deeply homophobic; in the revolution’s early days, gay men were sent to labor camps. Fidel Castro now publicly says he regrets that action.

Now there is more acceptance.

At the same time, the government controls virtually all real estate, and there are no gay bars or hotels.

Cruising men often have unsafe sex in abandoned buildings or parks where muggers lurk and the police conduct raids, said Libán Molina, 41, a volunteer at an AIDS prevention hot line.

Only about half of the 11,674 Cubans living with H.I.V. are now on antiretroviral drugs.

In theory, Cuba would be an ideal laboratory for “test and treat,” the new protocol in which patients who test positive go on drugs immediately to reduce by 95 percent their chance of infecting anyone else.

However, it requires modern drugs and Cuba makes only the older, harsher ones. Only about 1,100 patients get new drugs, paid for by foreign donors.

“We know about test-and-treat,” Dr. Pérez said. “We would do it, if we could. But we need the funds.”

**H.I.V./AIDS: Voices From Cuba (long)**

*By DONALD G. McNEIL Jr.*

**Published: May 7, 2012**

**Yudelsy Garcia O’Connor**

Yudelsy García O’Connor was the first known H.I.V.-positive baby in Cuba. Born Aug. 14, 1986, she is now 25 — tiny, but healthy. She is also lively, funny and irreverent, divorced and hoping to remarry and have children.

She was 3 before anyone realized that she was infected. Her father had been a soldier stationed in Angola. On his return in 1982, he worked as a truck driver, a job that helped him have girlfriends all over this island; he infected five of them.

Ms. García’s illness was discovered through a long line of contact-tracing. Her father had divorced her mother, but his second wife tested positive during a routine pregnancy screening. He was asked to name all his sexual partners, they and their children were tested.
Her growth was stunted, and she had anemia and lung problems. There were no drugs for AIDS at the time, but in 1990 she and her mother were moved to the country’s first sanitarium, in Santiago de Las Vegas, near Havana, and she grew up there.

“From the beginning, she captured our hearts,” Dr. Jorge Pérez Ávila, Cuba’s leading AIDS doctor, wrote in “AIDS: Confessions to a Doctor,” his memoir of his favorite patients, living and dead. “She was very thin, dark-haired, small and congenial, eager to play with anyone around.”

In 1993, when sympathetic Americans smuggled the experimental new drug AZT into Cuba, Ms. García was one of the first to get it.

When Cuba started producing its own basic AIDS drugs in 2001, she got triple therapy.

Now she has two modern drugs in her mix, thanks to the Global Fund to Fight AIDS, Tuberculosis and Malaria, which pays for some of the newer drugs that Cuba doesn’t make.

As a youngster, she was a poster child for the country’s effective AIDS program. She met the pope and former President Jimmy Carter.

But the system that sheltered her has now forgotten her.

At 21, she married another sanitarium resident and moved with him to his hometown — Aguacate, a flea-bitten place an hour’s drive from Havana where most residents work at a sugar refinery.

Her mother died in 2010, after she temporarily stopped taking her medicine. Then Ms. García’s husband left her; she tears up at any mention of that.

She now shares a one-bedroom shack in Aguacate with a friend. Her espresso pot has no lid. She turns on her hot plate by hooking two bare wires together.

She earns $8 a month overseeing a refinery vat, with a $10 bonus if she has no sick days.

It’s a long way from her happy sanitarium childhood; she is proud that she has her own place, but wishes she could afford to return to Havana.

**Enrique Lopez Vizcaíno**

Enrique Lopez Vizcaíno, 58, is a retired lieutenant colonel, an educator at the National Center for AIDS Prevention — and a medical marvel.

He was infected in 1977, four years before the “discovery” of AIDS was announced in an American medical journal’s article about unusual pneumonias in gay men.

He did not get antiretroviral drugs until 1996, but he is clearly a rare “slow progressor” — someone whose immune system is much better than average at fighting the virus.

He did have two bouts with leukemia, in 1991 and 2005, but it seems to be in remission.

Mr. Vizcaíno is certain of his infection date because of his sexual history. As a young lieutenant, he was stationed from 1976 to 1979 in Pointe Noire, Republic of Congo, as a military adviser to the Congolese army.

The only woman he slept with during those years, he said, was a Soviet woman, a language teacher also stationed there.

“AIDS was unknown at the time, of course,” he said, “but I was careful of Congolese women because there were many other diseases.”

Her name was Noema, but he could not recall her surname. During their affair, she taught him French and he taught her Spanish.

After his infection was diagnosed in late 1986, he wrote to her in Russia and they spoke on the phone. She said she had slept with Congolese men, he said. By 1986 she was already sick; she died in 1989.

As luck would have it, he did not pass on his infection to the first two girlfriends he had after returning home. But his third, whom he married, he did infect. They moved to a sanitarium together, and she died there in 1994.

Maria Elena Becquer lived in the same sanitarium and was recovering from a mastectomy. She also lost her spouse, who had become infected while stationed as a translator in Ethiopia.

“Slowly, our story began growing like a tree,” she said. “We had both lost someone important to us, and I saw he was a man who needed to keep living.”

Two years later, they were married. They remained in the sanitarium until 2003, when they found jobs as AIDS educators and moved to a sunny walk-up across the harbor from downtown Havana.

“It’s our little love nest.” Ms. Becquer said. “People say, ‘Oh, you were so unlucky to have all these diseases.’ But now all we ask is life — give us life to see our families, to finish our plans.”

**Carlos Emilio García**

Carlos Emilio García, 50, is both a nurse and a resident at the sanitarium in Santiago de Las Vegas.

When he is not on his shift in the small psychiatric ward, he lives in a neat bungalow he shares with a roommate. An advertising poster featuring a bare, soapy man dominates the tiled living room.
Four of his former roommates have left to live outside, but he chooses to stay. “My job is here, and I have everything I need,” he said. His family’s home is so crowded that he would have to share it with his parents, nine siblings, their children and some cousins. “We like living together, but there’s not much room,” he said. “Actually, I wish I could move some of them in here with me, but it’s not allowed.”

Also, he said, his salary is only $20 a month, too little to live on the outside. And even if he found a place, just getting through the paperwork of finding subsidized housing and being accepted by the local Committee for the Defense of the Revolution would take months.

At his previous hospital job, he had an AIDS test every six months from 1990 through 1996. But in 1997, right after he had a bout with nausea and diarrhea — a typical response to an early infection — he tested H.I.V.-positive.

Asked why a registered nurse who understood AIDS and had been tested many times would have sex without a condom, he shrugged, waved his hands in the air and said: “Oh you know — because we all do crazy things sometimes.”

Just once?, he was asked.

“Oh, no. Lots of times. I don’t know who my assassin was.”

Mariela Mendoza Ramos and Elio Bravo Ruiz

Mariela Mendoza Ramos, 58, and Elio Bravo Ruiz, 53, met and married at the Santiago de Las Vegas sanitarium. Both had become infected in Angola. She was a nurse-anesthesiologist in southern Angola, where the fighting against the South Africans was fiercest. He was a low-ranking soldier near the northern border, mostly doing guard duty. Like Mr. Vizcaino, he was one of the first Cubans infected, since he was in Angola from 1976 to 1981; in the national case log, he is Patient No. 20.

Mrs. Mendoza believes she was infected by one of many cuts and needle sticks she got then. “We were doing surgery in the jungle,” she said. “We didn’t even have gloves.”

He has no doubt he was infected by sex. “I was 18, I was unmarried, I was just a kid, I went with lots of women,” he said. “Nobody used condoms back then. Nobody had heard of AIDS.”

He was 25 when he was tested, he said. He had barely heard of AIDS and bristled when the doctors asked him if he was gay. The first years in the sanitarium were hard, he said; he was one of many apparently healthy young soldiers who had just been told they would be locked away for life.

Now he’s happy; he and his wife have one of the largest cabanas, with a garden full of flowers and a porch with lounge chairs and potted palms. Mrs. Mendoza said she her first husband was also a soldier stationed in Angola. In 1988, they were both tested on their return, and she was the only one infected. They divorced so she would not infect the man she still loved. They did it for the sake of their 8-year-old son, who had lived with his grandparents while they were overseas.

In those days, everyone died of AIDS, she said, “and there would be no one left to take care of our son.”

Maria Julia Fernandez Alvarez

Maria Julia Fernandez, 59, is the widow of Cuba’s Patient No. 1.

Although she has come to terms with her lot in life, she resents it. She has wrinkles now, and tires easily. Chemotherapy for abdominal cancer has robbed her of her hair — but the fiery eyes that made her a leader for many sanitarium patients are still blazing.

“I had only one man in my life, and after he died, I was afraid to have sex with any others,” she said. “And now I don’t think I will. And I never wanted to go to the sanitariums, but I had to live there for 10 years — at first by force, and then by circumstances.”

She spoke as she sat on the couch of her third-floor walk-up in downtown Havana. The building is dark and battered, but her apartment is spotless, with a view of the dome of the old Capitol, a gray copy of the one in Washington. Everything is pink: walls, curtains and bedspread, and bouquets of plastic flowers.

She met her husband, Reynaldo Morales, when they both worked at Granma, the party newspaper, she as a secretary, he as a driver for the editors. In 1984, he was sent to Angola.

“Yes, he ‘volunteered,’” she said, bitterly. “But you know what that meant back then. If you were connected to the party, and you didn’t ‘volunteer,’ it was a black mark on your record.”

He arrived home in 1986, just as Cuba bought its first AIDS tests. Though it later became clear that he was not the first Cuban infected, he was in the first group tested, and became Patient No. 1 in the national records. She was infected in the brief time they had together between his return and the test results coming back.
While she is serious, her husband was a practical joker, a buddy to everyone. He was first quarantined in a naval hospital with other soldiers, and used to describe how stir-crazy they went, smuggling in rum and once breaking out on a bedsheets rope. That April, Cuba opened its first sanitarium, and Maria and Reynaldo were the first couple admitted.

“Soldiers guarded us, and I didn’t see my son again until November, and then it was with a chaperon,” she said. “He was 9, and I had to accept seeing him once a week. I lost the nicest years of his life.”

Still, they had a cottage, and life inside was comfortable. Her husband became the compound’s carpenter and electrician. She formed the first patient group. It slowly won greater rights, including weekend passes without a chaperon.

“It was hard, but I learned to accept the irony of my life,” she said. “I was 32 when I went in, and absolutely homophobic: I came from a society very prejudiced against gay people, and soon most of the men inside were gay and the women were prostitutes. I had to share rooms, and a table, with these people. It was very, very hard. But I learned to love others for who they were.”

When the quarantine policy changed in 1993, she and Reynaldo were the first offered the chance to leave. But they declined. He felt useful and was surrounded by friends. He was also getting sicker and feared how people outside would look at him once word spread that he was dying of AIDS. He died in 1995, at the age of 42.

She moved out the next year. Her sister had lived in her apartment, and Granma had paid her $7-a-month salary during the decade she was inside, so she had enough saved to buy title.

She is now an educator at the national center for AIDS prevention. And she’s glad she no longer lives in the sanitarium.

“Life is out here,” she said.

**Lenia Cespedes Rodriguez**

Lenia Cespedes Rodriguez, 35, is one of a handful of Cubans infected by a blood transfusion.

In 1983, after President Fidel Castro ordered the country’s doctors to take steps to keep AIDS out of the country, one of their first moves was to throw out all imported blood; they discarded 20,000 units.

It seemed prudent since there was no test for H.I.V. and Cuba had no known AIDS cases, while Haiti did and had previously exported huge amounts of blood. In the United States and France, infected clotting factor ultimately killed most of a generation of hemophiliacs.

Since tests arrived in 1986, there have been 27 million transfusions in Cuba, with almost no transmissions.

Ms. Cespedes, a pricing expert for state stores, is an exception. In early 2002, she had surgery for an ectopic pregnancy and needed a transfusion. About a month later, a newborn transfused with blood from the same donor had a mysterious fever.

It turned out the baby was infected. The original donor apparently had been in the “window period” when the virus is in the blood, but antibodies have not yet formed.

Other than a fever 12 days after her transfusion — a typical reaction to a new H.I.V. infection — Ms. Cespedes has had no symptoms. Her CD4 count has stayed high enough that she was not put on medication under Cuba’s national treatment protocols.

Her first husband divorced her after she became infected. She and her second husband have always used condoms, she said, but now they want to have a baby. To drive down her viral load so there is virtually no chance she will infect him through unprotected sex, she began taking the drugs last spring.

Her bond with Dr. Pérez, who has overseen her treatment from the beginning, is obvious.

“She cries with me a lot,” he said. “She is more than a patient; we are friends.”

Ms. Cespedes confirmed that.

“If I have a boy, I’m going to name him Jorge,” she said.

And if it’s a girl?

“Jorgina.”

**HIV-Related Conspiracy Beliefs and Its Relationships with HIV Testing and Unprotected Sex Among Men Who Have Sex with Men in Tshwane (Pretoria), South Africa**

* AIDS Care Vol. 24; No. 4: P. 459-467, (04..2012) Waimar Tun; and others

The authors set out to determine the extent to which Pretoria MSM endorse HIV conspiracy beliefs. The team also sought to learn whether endorsing conspiracy beliefs about HIV is associated with never testing for the virus and with using condoms inconsistently.
Between February and August 2009, a cross-sectional survey was conducted using respondent-driven sampling. “A high proportion of respondents endorsed HIV conspiracy beliefs,” the authors reported. Fifty-one percent of MSM endorsed the belief that AIDS information is being withheld from the public; 25.5 percent endorsed the belief that HIV is a man-made virus; and about 20 percent endorsed the idea that humans are being used as guinea pigs in HIV treatment and research.

MSM who identified as bisexual or heterosexual were significantly more likely to endorse conspiracy beliefs compared to MSM who identified as homosexual (38.5 percent versus 14.7 percent). Endorsing HIV conspiracy beliefs was found to be significantly associated with not having undergone an HIV test (AOR: 2.4; 95 percent CI: 1.1–5.7); however, endorsement was not associated with engaging in unprotected anal intercourse.

“Endorsing beliefs in HIV conspiracies reflects a mistrust in government institutions and systems which could be an impediment to seeking HIV-related services, including HIV counseling and testing,” the authors concluded.

**UCLA life scientists unlock mystery of how 'handedness' arises**

The overwhelming majority of proteins and other functional molecules in our bodies display a striking molecular characteristic: They can exist in two distinct forms that are mirror images of each other, like your right hand and left hand. Surprisingly, each of our bodies prefers only one of these molecular forms.

This mirror-image phenomenon — known as chirality or "handedness" — has captured the imagination of a UCLA research group led by Thomas G. Mason, a professor of chemistry and physics and a member of the California NanoSystems Institute at UCLA.

Mason has been exploring how and why chirality arises, and his newest findings on the physical origins of the phenomenon were published May 1 in the journal *Nature Communications*.

"Objects like our hands are chiral, while objects like regular triangles are achiral, meaning they don’t have a handedness to them," said Mason, the senior author of the study. "Achiral objects can be easily superimposed on top of one another."

Why many of the important functional molecules in our bodies almost always occur in just one chiral form when they could potentially exist in either is a mystery that has confounded researchers for years.

"Our bodies contain important molecules like proteins that overwhelmingly have one type of chirality," Mason said. "The other chiral form is essentially not found. I find that fascinating. We asked, 'Could this biological preference of a particular chirality possibly have a physical origin?’"

In addressing this question, Mason and his team sought to discover how chirality occurs in the first place. Their findings offer new insights into how the phenomenon can arise spontaneously, even with achiral building-blocks.

Mason and his colleagues used a manufacturing technique called lithography, which is the basis for making computer chips, to make millions of microscale particles in the shape of achiral triangles. In the past, Mason has used this technique to "print" particles in a wide variety of shapes, and even in the form of letters of the alphabet.

Using optical microscopy, the researchers then studied very dense systems of these lithographic triangular particles. To their surprise, they discovered that the achiral triangles spontaneously arranged themselves to form two-triangle "super-structures," with each super-structure exhibiting a particular chirality.

In the image that accompanies this article, the colored outlines in the field of triangles indicate chiral super-structures having particular orientations.

So what is causing this phenomenon to occur? Entropy, says Mason. His group has shown for the first time that chiral structures can originate from physical entropic forces acting on uniform achiral particles.
Entire text is included in the image.
immune response by CD8 T cells. These cytotoxic T lymphocytes are thought to be responsible for controlling HIV infection.

In the current study, researchers analyzed data from male Step Study participants who enrolled in a trial that provided follow-up for up to four years after they enrolled in the Step study, or until Dec. 31, 2009, whichever came first.

The Step Study enrolled 3,000 male and female volunteers in North and South America, the Caribbean and Australia between 2004 and 2007. Injections in the study were halted in September 2007 after researchers detected a lack of effectiveness by the vaccine to prevent HIV acquisition or reduce HIV viral load in infected participants, and a higher-than-expected number of HIV infections in certain subgroups of vaccinees.

Journal Reference:

Dengue Infection and Miscarriage: A Prospective Case Control Study

Abstract

Background
Dengue is the most prevalent mosquito borne infection worldwide. Vertical transmissions after maternal dengue infection to the fetus and pregnancy losses in relation to dengue illness have been reported. The relationship of dengue to miscarriage is not known.

Method
We aimed to establish the relationship of recent dengue infection and miscarriage. Women who presented with miscarriage (up to 22 weeks gestation) to our hospital were approached to participate in the study. For each case of miscarriage, we recruited 3 controls with viable pregnancies at a similar gestation. A brief questionnaire on recent febrile illness and prior dengue infection was answered. Blood was drawn from participants, processed and the frozen serum was stored. Stored sera were thawed and then tested in batches with dengue specific IgM capture ELISA, dengue non-structural protein 1 (NS1) antigen and dengue specific IgG ELISA tests. Controls remained in the analysis if their pregnancies continued beyond 22 weeks gestation. Tests were run on 116 case and 341 control sera. One case (a misdiagnosed viable early pregnancy) plus 45 controls (39 lost to follow up and six subsequent late miscarriages) were excluded from analysis.

Findings
Dengue specific IgM or dengue NS1 antigen (indicating recent dengue infection) was positive in 6/115 (5.2%) cases and 5/296 (1.7%) controls RR 3.1 (95% CI 1.0–10) P = 0.047. Maternal age, gestational age, parity and ethnicity were dissimilar between cases and controls. After adjustments for these factors, recent dengue infection remained significantly more frequently detected in cases than controls (AOR 4.2 95% CI 1.2–14 P = 0.023).

Interpretation
Recent dengue infections were more frequently detected in women presenting with miscarriage than in controls whose pregnancies were viable. After adjustments for confounders, the positive association remained.

Plasma, Cervical HIV Load Often Discordant in 481-Woman US Group

Author: Mark Mascolini
08 May 2012

Plasma and cervical viral load were discordant (one detectable, the other not) in almost half of 959 clinic visits made by HIV-positive US women. Because it reduces plasma HIV load, combination antiretroviral therapy (ART) proved the most reliable predictor of cervicovaginal shedding.

A higher cervicovaginal viral load (CV-VL) raises chances of HIV transmission during sex. Plasma viral load usually correlates with CV-VL, but not always. US Women’s Interagency HIV Study (WIHS) researchers analyzed factors associated with CV-VL and plasma load in a large group of HIV-positive women.

During 959 clinic visits, CV-VL and plasma load were discordant at 450 visits (46.9%). In those 450 discordant visits, plasma load was detectable with undetectable CV-VL 435 times (45.3%), while CV-VL was detectable and plasma load undetectable in 15 visits (1.6%).
Lower CV-VL correlated with use of combination ART ($P = 0.01$), while higher CV-VL correlated with higher plasma load ($P < 0.001$), inflammation-associated cellular changes ($P = 0.03$), cervical ectopy ($P = 0.009$), exudate ($P = 0.005$), and trichomoniasis ($P = 0.03$). (Cervical ectopy is extension of cells that normally line the inside of the cervical canal onto the surface of the cervix, which makes them more vulnerable to infection. Exudate is fluid, such as pus or clear fluid, that leaks from blood vessels into nearby tissues.)

In 136 women with three or more clinic visits and detectable plasma load, multivariate analysis determined that the just-described factors correlated with increased CV-VL, as did friability (easily crumbled tissue) ($P = 0.05$).

Among women with an undetectable HIV load, decreased CV-VL correlated with use of combination ART ($P = 0.04$).

Analysis of these 136 women determined that 40.4% never shed HIV cervicovaginally, while 44.9% shed HIV intermittently. The rest shed HIV persistently.

Three factors raised the odds of more frequent shedding: higher initial plasma HIV load (odds ratio 2.47 per 10-fold higher), herpes simplex virus type 2 seropositivity (odds ratio 3.21), and alcohol use (odds ratio 2.20).

“Prediction of cervicovaginal HIV shedding solely on the basis of ART and plasma viral load is unreliable,” the researchers conclude.

“As a practical matter,” they add, “HIV-infected women should be counseled that cervicovaginal inflammatory conditions may increase risk of sexual transmission of HIV, and medical providers advised to diagnose and treat such conditions as a means of reducing HIV transmission.”


**FDA Favors First Drug for HIV Prevention**

*Associated Press*, (05.08.2012) Matthew Perrone

On Tuesday, Food and Drug Administration reviewers affirmed clinical trial data suggesting the HIV drug Truvada is safe and effective in cutting HIV infection risk when taken daily. The positive review comes ahead of an FDA advisory panel’s meeting on Thursday to discuss whether to approve Truvada for people at high risk of acquiring HIV sexually. The drug from Gilead Sciences already is approved to treat persons infected with HIV.

The panel will take separate votes on approval to market Truvada as an HIV prevention option among:

- gay and bisexual men,
- people in serodiscordant relationships and
- others at risk for acquiring HIV sexually.

Truvada only worked to prevent HIV when taken every day, reviewers emphasized. Adherence to the once-daily pill was less than perfect in clinical trials, which included condom use and HIV counseling, and adherence may be even less ideal in the real world, reviewers said.

Some researchers note that condoms are still the best prevention against HIV, and that a pill is not the same. Some drugs on the horizon also may prove to be better for HIV prevention than Truvada, which has had mixed results for preventing infection in women, critics say. Nonetheless, many advocates say Truvada should be an option, along with condoms, counseling, and other prevention measures.

Side-effects associated with Truvada include dizziness, diarrhea, nausea, and vomiting. More serious adverse events include liver toxicity, bone thinning, and kidney problems.

FDA does not have to follow the advice of its advisory panels, but usually does so.

**The UCLA Sex Squad Is Here to Help**

*The Advocate*, (05.03.2012) Neal Broverman

A University of California-Los Angeles performance troupe’s lighthearted, humorous and open approach to sexual health matters recently had a ninth-grade audience interacting and laughing. Unusually, no one was texting. The UCLA Sex Squad, part of the Art and Global Health Center’s “AMP It Up!” project, regularly performs at local high schools, discussing safe sex and involving students in related art projects, including poetry, skits, and visual arts. An audition is required to join the Sex Squad.
The high-school performances include Sesame Street spoofs using condom puppets talking about the correct use of condoms, and discussions of physically and emotionally fulfilling sex, masturbation, orgasms, how alcohol can impair judgment, and informative personal stories about squad members’ first-time sex experiences, as well as interactive songs about the ways HIV can be transmitted.

HIV testing increased more than three-fold, from 14 percent to 59 percent, among sexually active students offered screening during the AMP It UP! programs, one study found.

“That’s what we want to see,” said David Gere, the health center’s founder and director, and brother of actor Richard Gere. “It indicates a belief that it’s important to know your status.”

Gere and center staffer Bobby Gordon recently hit the road to help bring the UCLA Sex Squad model to Southern high-school students. The two worked with Emory University in Atlanta and the University of North Carolina-Chapel Hill to create troupes that will be adapted to their local environments. Gere and Gordon are confident the program will succeed in other parts of the country.

**Millennium Villages Project Research Yields Positive Results, But Some Researchers Question Methods Used**

"Death rates among children under five at the [Millennium Villages Project (MVP)]—set up in Africa to demonstrate what is possible if health, education, agriculture, and other development needs are tackled simultaneously—have fallen by a third in three years compared with similar communities, according to the project’s first results," published in the Lancet on Tuesday, the Guardian reports (Boseley, 5/8). The study "offers quantitative evidence of the success of the MVP model at nine Millennium Village sites in sub-Saharan Africa," Nature News writes, adding, "Between 2006 and 2009, mortality in under-fives fell by an average of 22 percent, reaching a level roughly two-thirds of that in control villages not involved with the project, where child mortality seemed to rise."

"But some researchers have questioned the methods used to quantify the benefits of the project, and demanded that the MVP release its underlying data," the news service notes. Michael Clemens, a migration and development researcher at the Center for Global Development, "says that these headline figures are misleading for a number of reasons," and notes "the control-village data include retrospectively estimated figures that are probably too high"; "nationwide improvements in child mortality over the three years of the study were almost as good as in the Millennium Villages"; and "deriving trends from children monitored in a few villages for just three years introduces significant statistical uncertainty" (Gilbert, 5/8).

**Treatable Infections Responsible For Nearly 2M Cases Of Cancer Globally Each Year, Study Suggests**

"Bacteria, viruses and parasites cause around two million cases of cancer in the world each year, experts believe," the Press Association/Guardian reports. According to the news service, "Scientists carried out a statistical analysis of cancer incidence to calculate that around 16 percent of all cancers diagnosed in 2008 were infection-related," and "[t]he proportion of cancers linked to infection was three times higher in developing countries than in developed ones."

Four "[k]ey cancer-causing infectious agents"—including human papillomavirus (HPV), the gastric bug Helicobacter pylori, hepatitis B virus (HBV), and hepatitis C virus (HCV)—"were together believed to be responsible for 1.9 million cases of cancer, mostly gastric, liver and cervical cancers," the news service writes. "Dr. Catherine de Martel and Dr. Martyn Plummer, from the International Agency for Research on Cancer in Lyon, wrote in the Lancet Oncology journal: 'Infections with certain viruses, bacteria, and parasites are one of the biggest and preventable causes of cancer worldwide. ... Application of existing public health methods for infection prevention, such as vaccination, safer injection practice, or antimicrobial treatments, could have a substantial effect on future burden of cancer worldwide,'" the Press Association notes (5/9).

**Leishmaniasis Vaccine Trial Begins In U.S., India**

"A vaccine against one of the most neglected yet fatal tropical diseases is being tested for the first time in a clinical trial in India and the U.S.," IRIN reports. Visceral leishmaniasis (VL), "also called kala-azar or black fever, infects an estimated half million persons or more annually," and "[i]t is found most commonly in India, Nepal, Bangladesh, Brazil and Sudan," the news service notes. "A total of 72 volunteers are participating in the trial, but scientists say it will take years of testing to roll out an affordable vaccine to the 200 million people globally at risk of VL infection," IRIN writes, adding, "The WHO has warned that..."
VL is spreading to previously unaffected countries due to co-infections of HIV and leishmaniasis, while the Intergovernmental Panel on Climate Change (IPCC) has said climate change can also spur the spread of the disease" (5/9).

**Soybeans soaked in warm water naturally release key cancer-fighting substance**

Soybeans soaking in warm water could become a new "green" source for production of a cancer-fighting substance now manufactured in a complicated and time-consuming industrial process, scientists are reporting in ACS' *Journal of Agricultural and Food Chemistry*.

Hari B. Krishnan and colleagues explain that the substance, Bowman-Birk Protease Inhibitor (BBI), has shown promise for preventing certain forms of cancer in clinical trials. Those human tests resulted from evidence of BBI's beneficial effects, including indications that BBI derived from the large amounts of soybeans in traditional Japanese diets might underpin low cancer mortality rates in Japan. However, the current method of extracting BBI from soybeans is time-consuming and involves harsh chemicals. The scientists set out to see if there might be a greener and more environmentally friendly way of obtaining BBI.

They found that soybean seeds incubated in water at 122 degrees Fahrenheit naturally release large amounts of BBI that can easily be harvested from the water. The protein appeared to be active, with tests showing that it stopped breast cancer cells from dividing in a laboratory dish. "The abundance of BBI in soybean seed exudates by incubating the seeds in warm water provides a simple and alternative method to iso

**It's a Trap: New Lab Technique Captures microRNA Targets**

ScienceDaily (May 9, 2012) — Human cells are thought to produce thousands of different microRNAs (miRNAs)—small pieces of genetic material that help determine which genes are turned on or off at a given time. miRNAs are an important part of normal cellular function, but they can also contribute to human disease—some are elevated in certain tumors, for example, where they promote cell survival. But to better understand how miRNAs influence health and disease, researchers first need to know which miRNAs are acting upon which genes—a big challenge considering their sheer number and the fact that each single miRNA can regulate hundreds of target genes. Enter miR-TRAP, a new easy-to-use method to directly identify miRNA targets in cells.

This technique, developed by Tariq Rana, Ph.D., professor and program director at Sanford-Burnham Medical Research Institute (Sanford-Burnham), and his team, was first revealed in a paper published May 8 by the journal *Angewandte Chemie International Edition*.

"This method could be widely used to discover miRNA targets in any number of disease models, under physiological conditions," Rana said. "miR-TRAP will help bridge a gap in the RNA field, allowing researchers to better understand diseases like cancer and target their genetic underpinnings to develop new diagnostics and therapeutics. This will become especially important as new high-throughput RNA sequencing technologies increase the numbers of known miRNAs and their targets."

**How miR-TRAP works**

miRNAs block gene expression not by attaching directly to the DNA itself, but by binding to messenger RNA (mRNA), the type that normally carries a DNA recipe out of the nucleus and into the cytoplasm, where the sequence is translated into protein. Next, these RNAs are bound by a group of proteins called the RNA-induced silencing complex, or RISC. This blocks production of the protein encoded by that mRNA, an action that can have far-reaching consequences in the cell.
miR-TRAP is performed in three basic steps. Scientists 1) produce highly photoreactive probes by conjugating psoralen, a plant molecule that can be activated by light, to an miRNA of interest, 2) perform a long-wave UV photocrosslinking reaction, and 3) pull down RNA and analyze it by RT-qPCR. In other words, researchers zap cells with UV light, freezing the miRNA/mRNA duo in place. Then, after extracting the RNA from the cells, they can take a closer look at the sequence of the bound mRNA, revealing the miRNA’s target gene.

**Advantages of miR-TRAP**

miR-TRAP is easier and more accurate than current methods of identifying miRNA targets for three main reasons. First, miR-TRAP can directly identify miRNA targets in live cells, under normal or disease conditions. Second, this technique can spot mRNA targets that are not only reduced by miRNAs, but also those whose translation into protein is repressed—targets that aren’t normally picked up by other techniques, such as qPCR or microarray analysis. Third, miR-TRAP doesn’t rely on antibodies, which can lead to nonspecific background signals and complicate data interpretation.

Putting miR-TRAP to the test, Rana and his team, including postdoctoral researcher Huricha Baigude, Ph.D., analyzed 13 predicted targets of two important microRNAs. The technique not only confirmed their known gene targets, but also revealed two novel targets.

“We’re now applying these methods to identify miRNA targets in a number of disease models,” Rana said. “And it’s our hope that miR-TRAP will soon become common practice in many labs around the world.”

**Journal Reference:**


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**Immune System: How Memory B Cells Stay 'in Class' to Fight Different Infections**

*ScienceDaily (May 7, 2012) — Scientists at The Scripps Research Institute have made an important discovery about the internal programming of B cells, the immune cells that make antibodies against infections. The finding opens the way for the development of vaccines that can work more efficiently and hint at therapies for conditions in which B cells cause harm—such as the autoimmune disease lupus erythematous, severe allergies, and B-cell lymphomas.

The discovery reveals that B cells produce special proteins to maintain themselves in a particular functional "class," even as they lie dormant in the memory-cell state, awaiting a new infection. The class of a B cell determines how its antibodies marshal other components of immunity, and thus how well they can remove a certain type of threat, say bacteria on the skin versus intestinal parasites.

"This is a real breakthrough, in the sense that we now have a much better understanding of how B cell class is regulated, and how we might target that regulatory process in vaccine and drug design," said Michael McHeyzer-Williams, a Scripps Research professor who was the principal investigator for the study, published in *Nature Immunology*’s advance online edition on May 6, 2012.

**Specialized Infection Fighters**

Young, "naïve" B cells begin their careers as infection fighters when they are exposed, in the right way, to pieces of an invading microbe that happen to match their main receptor (the B cell receptor, or BCR). Some then become plasma B cells, and slowly ramp up the active production of antibodies. Others instead become memory B cells, which can lie in wait for years, primed to respond very rapidly and nip in the bud any reinfection.

Either way, as B cells move out of the naïve state, helper T cells secrete chemical signals that typically force the B cells into particular classes. IgG-class B cells are the most common in humans, and are broadly effective against viruses and bacteria. IgA-class B cells are predominantly found on mucosal surfaces such as in the throat and intestines. IgE-class cells and their antibodies protect against intestinal worms and other parasites. Some B cells stay in the default IgM class. The class of a B cell is marked by the type of "stem" it has on its Y-shaped antibodies; this stem, or effector, can mobilize other elements of the immune system, such as inflammatory chemicals, when the antibody binds to an invader.

It had been long assumed that the switching of a B cell to a particular class is the result of a one-time signaling event. "The idea was that the signals that produce this switch don't persist in B memory cells, for example," said Nathaniel Wang, a graduate student in the McHeyzer-Williams laboratory who was first author of the new study.

**Testing Assumptions**

In the study, Wang, McHeyzer-Williams, and their colleagues tried to determine whether that assumption is true. They knew, for example, that when T cells cause naïve B cells to switch to the IgG2a class, a potent
antiviral class, they do so by inducing the production in B cells of a particular protein called T-bet. To clarify T-bet’s role, the researchers engineered transgenic mice whose B cells lack the protein.

Without T-bet, they found, the mouse B cells could not be switched to the IgG2a class, even when presented with all the normal stimuli, and even though other IgG classes could be produced normally—or even in higher amounts. Even more surprisingly, in existing IgG2a memory B cells, the abrupt knockdown of T-bet levels caused the cells to lose their ability to respond to a new infection. In fact, most of the T-bet-deprived memory B cells became undetectable within a few days.

"T-bet turns out to be the central molecule that enforces the IgG2a class in B cells, and if its production stops in IgG2a memory cells, they become dysfunctional and die," Wang said.

The finding that T-bet has this all-important, ongoing function in IgG2a memory cells suggested that other proteins play analogous roles in other classes of memory B cell. Wang therefore turned to memory B cells of the IgA class, and, with a similar set of experiments, showed that these memory B cells depend on the transcription factor RORα. "It essentially does for IgA memory cells what T-bet does for IgG2a memory cells," said Wang.

**Implications for Science and Medicine**

Wang and McHeyzer-Williams and their colleagues are now searching for the proteins that keep other memory B cells healthy and in their classes. But already the work has clarified how memory B cells work. "Until now we haven’t really had a good conceptual framework for the development and maintenance of these cells," McHeyzer-Williams said.

The findings clearly also have implications for medicine. By supplying a particular class-enforcement protein at the same time that it exposes B cells to microbial proteins, a vaccine could induce a long-term immunity that is heavily weighted towards a desired antibody class. "If you’re designing a vaccine for certain types of virus, for example, you would like to have lots of IgG2a and IgA memory cells," said McHeyzer-Williams. "So the goal would be to design a chemical adjuvant for the vaccine that drives B cells into those classes."

Similarly, therapies that knock down class-enforcement signals such as T-bet could usefully reduce or eliminate memory B cells in certain classes. "Some autoimmune, allergic and lymphoma conditions are driven by B cells of a particular class, for example IgE cells in allergies," said McHeyzer-Williams. "Being able to target just that class of B cell would be an obvious advantage over existing therapies, such as steroids, that knock down large parts of the immune system."

**Journal Reference:**


**Allergies: Gut Flora Affects Maturation of B Cells in Infants**

ScienceDaily (May 7, 2012) — Infants whose gut is colonized by *E. coli* bacteria early in life have a higher number of memory B cells in their blood, reveals a study of infants carried out at the Sahlgrenska Academy at the University of Gothenburg, Sweden.

The bacteria in our gut outnumber the cells in our bodies by a factor of ten and are extremely important for our health because they stimulate the maturation of the immune system. The normal bacterial flora in the gut is established at the very beginning of our lives, but an increasingly hygienic lifestyle has led to changes in this flora.

**Colonised ever later**

These days Swedish children are colonized by *E. coli* bacteria later and later. They also have a less varied bacterial flora and a smaller turnover of bacterial strains in the gut than children in developing countries. Meanwhile, diseases caused by deficiencies in immune regulation have increased sharply, making allergies a major public health issue in the Western World.

**B cells play key role in development of allergies**

Researchers at the University of Gothenburg’s Sahlgrenska Academy have looked at B cells, a type of white blood cell that produces antibodies that can protect the body against infection and play a key role in the development of allergies. By studying 65 healthy newborn babies in the Västra Götaland region, researcher Anna-Carin Lundell and her colleagues were able to show that infants whose gut is colonized by *E. coli* bacteria during the first few weeks of life had a higher number of memory B cells at the age of both four and 18 months.
"The results are important for understanding the relationship between our complex bacterial gut flora and our immune system, and show what we risk losing with an excessively hygienic lifestyle," Anna-Carin Lundell explains.

"Most of the bacteria around us are harmless, and we should see them as a very important form of training so that our children’s immune systems mature properly. Healthy newborns should not be over-protected against natural exposure of the gut flora."

**Journal Reference:**

**HIV–HBV Coinfection — A Global Challenge**
Athena P. Kourtis, M.D., Ph.D., M.P.H., Marc Bulterys, M.D., Ph.D., Dale J. Hu, M.D., M.P.H., and Denise J. Jamieson, M.D., M.P.H.


Human immunodeficiency virus type 1 (HIV-1) and hepatitis B virus (HBV) exact a high toll worldwide. Both can lead to chronic disease, cancer, and death, and neither can be eradicated with the use of current therapies. Antiviral drug resistance often develops after patients have received treatment for some time and is usually followed by the loss of clinical benefit. Coinfection with the two viruses exacerbates the negative effects.

Worldwide, HBV is the leading cause of chronic liver disease and a leading cause of death, accounting for up to half of all cases of cirrhosis and hepatocellular carcinoma. An estimated 400 million people are infected with HBV, with the majority of cases occurring in regions of Asia and Africa where the virus is endemic. There, up to 70% of adults show serologic evidence of current or prior infection, and 8 to 15% have chronic HBV infection.

These staggering infection rates largely reflect a failure of maternal and child health programs. The majority of HBV infections in settings where the virus is highly endemic occur through perinatal transmission (predominant in East and Southeast Asia) or in young children, transmitted through close household contact or through medical or traditional scarification procedures (predominant in Africa). Perinatal HBV infection is associated with a 90% risk of chronic hepatitis B, as compared with a risk of less than 5% among adults with intact immunity. The risk of perinatal transmission is lower in Africa than in Asia, a disparity that could be due to a lower prevalence of hepatitis B e antigen (HBeAg) and other differences in the pathogenic characteristics of circulating HBV genotypes.

According to the Joint United Nations Program on HIV/AIDS (UNAIDS), about 33 million people are infected with HIV worldwide, and the majority of them live in Asia and Africa. Approximately 10% of the HIV-infected population has concurrent chronic hepatitis B, with coinfection more common in areas of high prevalence for both viruses. In countries where the viruses are highly endemic, the rate can be as high as 25%. In areas where HBV is less endemic (North America, Europe, and Australia), HBV and HIV are most often acquired during adolescence or adulthood through sexual transmission or injection-drug use. The prevalence of HIV–HBV coinfection in these regions is generally less than 10% of the HIV-infected population. However, up to half of injection-drug users infected with HIV are coinfected with HBV. Worldwide, there may be 3 to 6 million HIV-infected people living with chronic HBV.

HIV–HBV coinfection increases the morbidity and mortality beyond those caused by either infection alone. People coinfected with HIV have higher levels of hepatitis B viremia, have progression to chronic hepatitis B that is approximately five times as fast as that among people infected with only HBV, and have a higher risk of cirrhosis and hepatocellular carcinoma. HIV immunosuppression can even cause the loss of hepatitis B surface antibodies and reactivation to chronic hepatitis B. As compared with healthy, uninfected persons, those infected with HIV — particularly the most immunocompromised — mount poorer antibody responses to HBV vaccination. Managing hepatitis B in HIV-coinfected patients is further complicated by the dual activity of several nucleoside analogues, the emergence of resistant HIV or HBV strains, the limitations of and decreased response to interferons, and the more rapid development of lamivudine-resistant HBV.

Very few studies have addressed coinfection with HBV among HIV-infected pregnant women. Studies in Africa indicate that they are three times as likely as HIV-negative pregnant women to test positive for HBV DNA and twice as likely to test positive for HBeAg. Both higher HBV DNA levels and HBeAg
expression are associated with an increased risk of an HIV-infected pregnant woman’s transmitting HBV to her child.1

Vaccination of infants against hepatitis B is highly protective, reducing the risk of infection by more than 70% (the addition of hepatitis B immune globulin reduces the remaining risk by half. However, many countries with a high prevalence of HBV lack universal or timely vaccination coverage, and hepatitis B immune globulin is often unavailable or prohibitively expensive. In 2006, for example, the coverage rate for the vaccine dose at birth was only 36% in countries where the prevalence of chronic HBV infection exceeded 8%.

Even with appropriate vaccination, 5 to 15% of infants born to mothers who test positive for hepatitis B surface antigen (HBsAg) become infected. The proportion is much higher among infants whose mothers have high serum HBV DNA levels; transmission rates of 30% or higher have been noted.3 High HBV DNA levels are often seen in women with concurrent HIV infection, particularly in Southeast Asia, where HBV is highly endemic and perinatal transmission of HBV is already common.

Additional approaches are needed to protect children of infected mothers. For example, the use of antiviral therapy in pregnant women with high HBV loads has been examined in a few small studies and has shown promise in decreasing perinatal transmission;3 this strategy appears to be cost-effective and should be explored further.4 Women coinfected with HIV would be good candidates for this preventive approach.

Even in areas with historically low rates of HBV, challenges exist. In the United States, the number of HBV-infected pregnant women is probably underestimated, with current methods relying on the expectation that certain ethnic groups are at high risk. In Europe, there is no consistent policy of testing women for HBV infection during pregnancy; some countries rely on assessment of “risk factors” alone. Immigration patterns in Europe and North America suggest that HBV prevalence will vary by region.

There are a number of unanswered questions about disease pathogenesis in coinfected persons and the management of HIV–HBV coinfection, especially in pregnant women. Pregnancy itself can trigger elevations of liver enzymes. The administration, during pregnancy, of antiretroviral prophylaxis containing one agent with anti-HBV activity may be associated with later development of HBV resistance. For pregnant women who, to prevent perinatal HIV transmission, take antiretroviral prophylaxis containing one or two agents with anti-HBV activity, the safety of stopping treatment after delivery is unknown. The administration of antiretrovirals without HBV activity in coinfected pregnant women may leave their infants unprotected against HBV. Finally, infection of the infant with HIV threatens the benefits of HBV immunization for perinatal prevention.

What will it take to address this crisis? First, we must acknowledge that HBV–HIV coinfection represents a major global public health threat. Because each virus affects the other’s natural history and response to therapy, HIV–HBV coinfection requires dedicated research. A willingness to rapidly implement new scientific evidence is critical. Preventing transmission of both viruses to the next generation should be a priority for health policymakers.

Ideally, all pregnant women should receive early prenatal care with voluntary HIV and HBV testing to permit timely interventions aimed at preventing perinatal transmission.5 Use of antiretroviral agents with dual antiviral activity is a promising preventive approach — one limited, however, by a paucity of data on important agents (e.g., tenofovir) regarding safety during pregnancy, for both the fetus and the mother. As regimens including tenofovir become first-line therapy for many HIV-infected people (and are used as preexposure prophylaxis for the uninfected), determining the safety of these medications during pregnancy becomes a critical research need. Evaluating the HBV viral load in HIV-infected pregnant women should be an essential step of prenatal evaluation, so that the mother’s health can be managed appropriately.

Continued improvements in the coverage and timeliness of HBV vaccination and the education of clinicians about its importance should be priorities everywhere. Making such improvements will require substantial advocacy and political and financial commitment. Now is the time to provide the best care we can for coinfected people and to protect a future generation of children from the largely hidden epidemic of HBV-related liver disease, which is being further fueled by the HIV epidemic.
HIV treatment reduces incidence of pre-cancerous cervical lesions and promotes their regression

Michael Carter
Published: 10 May 2012

Antiretroviral therapy is associated with a reduced incidence of pre-cancerous cervical lesions in HIV-positive women, South African investigators report in the online edition of AIDS. Their study also showed that HIV therapy was associated with a regression of pre-existing lesions.

“Our results indicate that compared to non-HAART [highly active antiretroviral therapy]-users, HIV-infected women on HAART are more than twice as likely to exhibit regression of cervical lesions,” write the authors. “HAART users with baseline normal cervical smears are significantly less likely to suffer from incident abnormalities in subsequent cervical smears.”

Cervical cancer has been classified as an AIDS-defining illness since 1993. Most diagnoses involve HIV-positive women in resource-limited settings, especially sub-Saharan Africa.

The malignancy is caused by high-risk strains of human papilloma virus. This sexually transmitted infection can cause pre-cancerous cell changes in the cervix and other anogenital sites.

Incidence of the other AIDS-defining cancers – non-Hodgkin’s lymphoma and Kaposi’s sarcoma – has fallen significantly since the introduction of effective antiretroviral therapy. This treatment has also been associated with the regression of disease caused associated with these cancers.

However, the benefits of HIV therapy regarding prevention of cervical cancer are less clear. To establish a clearer understanding of its potential benefits, an international team of investigators designed a study involving 1123 HIV-positive women in Soweto, South Africa, who had at least two cervical smears between 2003 and 2009.

Their research had two aims:

- To compare the incidence of abnormal cervical smears in women with normal results at baseline according to the use or non-use of HIV therapy.
- To assess the association between HIV treatment and the regression/progression of cervical lesions.

The patients had a mean baseline age of 33 years. Their mean body mass index (BMI) was 26.8. Smoking – a risk factor for cervical cancer – was reported by 15% of women. Symptoms of a sexually transmitted infection were detected in 18% of women when they entered the study, at which time 75% of participants had a current sexual partner.

Only 2% of individuals were taking HIV therapy at baseline, a further 17% starting treatment during follow-up.

The number of cervical smears per patient ranged from two to seven with an average of three. The median interval between consecutive smears varied from 181 to 2343 days, the median interval being 421 days.

Taking antiretroviral therapy reduced the risk of incident cervical lesions.

Women who had a normal cervical smear at baseline were 38% less likely to develop an abnormality if they were taking HIV therapy (p = 0.001).

A low CD4 cell count was associated with an increased risk of developing abnormal cells. This was irrespective of treatment with antiretroviral drugs. Incident lesions were twice as likely to be detected in women with a CD4 cell count below 200 cells/mm³ compared to women with a CD4 cell count above 500 cells/mm³ (p = 0.001). Smoking was also associated with an increased risk of new cervical disease (p = 0.05).

There was some evidence that antiretroviral treatment was associated with a reduced risk of the progression of cervical lesions. After taking into account other possible risk factors, the investigators found that HIV therapy reduced the risk of progression by 20%. However, this fell short of significance (95% CI, 0.56-1.13; p =0.20).

In contrast, HIV treatment was associated with the regression of lesions. The odds of regression were over twice as high for individuals taking antiretroviral therapy (OR = 2.61; 95% CI, 1.75-3.89; p < 0.001).

“We found that women on HAART were more than twice as likely than non-HAART users to demonstrate regression in consecutive smears,” conclude the authors. “In addition, we found that among those women with a baseline normal smear, those on HAART were significantly less likely to develop an abnormality in the future.”

Reference
Potential for Risky Sex Spurs Discord on HIV Prevention Pill

*Bloomberg News*, (05.09.2012) Ryan Flinn; Shannon Pettypiece
AIDS advocates are divided about whether the potential approval of the first pill to prevent HIV infection will advance public health efforts to curb the epidemic.

The Food and Drug Administration is considering whether to approve Gilead Sciences Inc.’s Truvada for groups at high risk of HIV infection. A study cited by FDA shows it can reduce the risk of HIV by up to 94 percent for people who took the pill as prescribed. However, other trials indicated just 10 percent of participants adhered to prescribing instructions, and one study was halted after no benefit was seen. The $14,000-a-year drug is already approved for treating HIV infection.

“Among our own patients who are HIV-positive, we have difficulty getting them to adhere, let alone people who don’t have the disease,” said AIDS Healthcare Foundation President Michael Weinstein. AHF provides medical care for 130,000 patients worldwide.

Some advocates worry Truvada’s approval could encourage unprotected sex. “If you have this new option, would you be riskier? There is no evidence to show that might be the case, but that doesn’t mean it’s not a concern,” said Mitchell Warren, executive director of AVAC: Global Advocacy for HIV Prevention.

James Loduca, spokesperson for the San Francisco AIDS Foundation, said approving Truvada as a pre-exposure prophylaxis would help certain people avoid infection during particular times in their lives. “We don’t think PrEP is a lifetime prevention tool,” he said. “It would be used in a targeted way for specific population and in relatively short periods of time.”

“If deployed correctly and efficiently, it could make a big dent in the epidemic in the US,” said Howard Jaffe, president and chair of the Gilead Foundation.

HPV Vaccine: Fewer Girls Getting All Three Doses

*Washington Post*, (05.03.2012) Jennifer Huget, The Checkup blog
New research shows a decline in the number of females receiving all three doses of the human papillomavirus vaccine between 2006, when it was approved, and 2009.

Abbey Berenson and Jacqueline Hirth of the University of Texas Medical Branch and co-investigators studied data for nearly 272,000 privately insured females who started the vaccine series. While the overall number of girls who received the first shot in the series rose during the study period, the percentages of those who got all three dropped from roughly 50 percent in 2006 to just over 20 percent in 2009.

Females age 13 and older were less likely than those ages nine to 12 to receive all three shots. Females who completed the series were more likely to have been vaccinated by their OB/GYN than by their pediatrician.

The second dose of HPV vaccine should be given one to two months after the first, with the third and final shot administered within six months of initiation. Yet just over 38 percent who got the first shot completed the series within one year. The study did investigate the reasons for non-completion.

Berenson said a goal of the study was to alert parents to the importance of getting all three shots. According to the researchers, physicians may not be doing enough to ensure that the series is completed. And the marketing campaign that began in 2006 “never addressed the three shots,” said Berenson. The website for Gardasil, one of two approved HPV vaccines, does note that the immunization is given in three shots.

[PNU editor’s note: The study, “Completion of the Human Papillomavirus Vaccine Series Among Insured Females Between 2006 and 2009,” was published in the journal Cancer (2012;doi:10.1002/cncr.27598).]

Condom Use During Most Recent Anal Intercourse Event Among a US Sample of Men Who Have Sex with Men

*Journal of Sexual Medicine Vol. 9; No. 4: P. 1037-1047*, (04..2012) Joshua G. Rosenberger, PhD, MPH; and others
The researchers set out to determine the demographic and event-specific situational factors associated with condom use during the most recent penile-anal intercourse (PAI) event among MSM. They noted that recent nationally representative data on event-level condom use have included samples that are predominantly heterosexual, yielding limited information on condom use rates for PAI among MSM.

An Internet survey collected data from 14,750 MSM (ages 18-87) in the 50 US states and the District of Columbia. The main outcome measures included factors related to sociodemographics, recent sexual
behavior history, event characteristics, use of condoms and items associated with ejaculation during the encounter.

Most of the men (85.3 percent) identified as homosexual. Their median age was 39; 83.2 percent were white; 7.2 percent were Latino; and 3.9 percent were African-American.

Among the men, only 2.5 percent reported that their most recent PAI involved ejaculation without a condom in their anus or their partner’s anus. Age, race/ethnicity, partner status, and location of the sexual event (all P=0.001) were found to be significantly related to the likelihood of condom use during the most recent PAI with a man.

“This study provides a large-scale assessment of condom use during the most recent PAI among MSM in the United States,” the authors concluded. “Findings from this study highlight diversity in condom use behaviors and demonstrate varying degrees of potential risk for [HIV] and other [STIs]. Future prevention efforts should consider contextual components of condom use, including partner type, location of the sexual event and semen exposure, to more accurately develop individualized risk reduction strategies.”

‘Gut’-throat competition: Research on digestive tract bacteria yields surprising findings
Native bacteria help fend off invaders, study finds – suggesting ways to prevent or treat the effects of some dangerous forms of E. coli
ANN ARBOR, Mich. — From tiny villages in developing nations to suburban kitchens in the United States, dangerous strains of E. coli bacteria sicken millions of people each year — and kill untold numbers of children.

Now, new research from the University of Michigan Health System gives scientists a better understanding of what is going on in the diarrhea-wracked guts of its victims, and what might be done to prevent or treat it.

Specifically, they show that the bacteria that usually live in our digestive tracts compete against invading bacteria such as E. coli to help our bodies fend them off.

They also show that the invaders depend on certain genes to gain a temporary upper hand in that battle — just long enough to reproduce and cause the symptoms that expel their offspring from the body so they can find a new host.

The findings, published in journal Science on its Science Express website, point to potential ways to prevent or treat infections by enterohemorrhagic or enteropathogenic E. coli: Those are the types that can lurk in undercooked ground beef, unpasteurized milk, untreated drinking water, and contaminated produce — and that can cause diarrhea and other symptoms that sicken adults and can kill vulnerable children.

"More than 1,000 species of bacteria live in our guts, in a symbiotic population called the microbiota," says Gabriel Nunez, M.D., the U-M pathologist who led the research team. "These results show that these bacteria, also called commensals, compete with pathogens (disease-causing bacteria) in a previously unappreciated way — and that the pathogens use a specific set of genes to temporarily outcompete commensals before leaving the body. Understanding this gives us potential targets for prevention and treatment."

For instance, since the research shows that harmful bacteria compete with commensal bacteria for certain nutrients that they need to survive, selectively removing some nutrients and boosting others might help. So might a more targeted use of antibiotics when treating patients who are battling an E. coli infection.

Nunez and first author Nobuhiko Kamada, Ph.D., a postdoctoral fellow, made the findings by studying mice that they infected with C. rodentium — the rodent equivalent of harmful E. coli. The study
included specially bred germ-free mice that lacked all the "good" gut bacteria that normal mice and humans harbor.

Both Nunez and Kamada are members of the U-M Medical School's Department of Pathology and the U-M Comprehensive Cancer Center, and the work fits into their broader investigations of how inflammation and immunity play a role in the body's response to cancer as well as infections.

Fittingly, Nunez holds the Paul H. de Kruif Professorship in Pathology, named for the U-M graduate who wrote Microbe Hunters, a pivotal 1926 book on the history of infectious disease research.

In the new paper, the team adds a new chapter to the understanding of how pathogenic bacteria gain a foothold in the gut – literally – by turning on virulence genes that allow them to attach to the cells that line the digestive tract.

This attaching-and-effacing activity, as it is called, allows the disease-causing bacteria to intimately adhere to the cells that line the gut, consume nutrients and reproduce, out-competing the natural gut bacteria. But this comfortable niche only lasts a few days or weeks, during which the host's gut gets more inflamed as the immune system responds to the insult. Diarrhea, sometimes containing blood that leaks from the gut lining, results.

And that, the researchers find, is when the pathogens stop expressing the virulence genes that allowed them to gain their upper hand. They unhitch from the gut lining, mixing in with the commensal bacteria in the open center (lumen) of the gut, and fighting for what food they can find.

While this return to competition means that some of them die, enough of them survive to be expelled in the feces. And if good sanitation systems aren’t in place, the bacterial offspring have a great chance of finding a new host to take a toll on.

Better sanitation throughout the world can prevent infections in the first place, says Nunez. But when infection by pathogenic bacteria occurs, a better understanding of the way they interact with our native bacteria could eventually help save lives.

Nunez’s team is working with the lab of U-M microbiologist and co-author Eric Martens, Ph.D., to screen different sugars that, if withheld or enhanced in the diet, might weaken the pathogens’ effects. That could lead to a better understanding of how children and weak adults in developing nations should be fed while being treated for infection.

The University of Michigan has applied for patent protection, and is in the process of looking for commercialization partners to help bring the technology to market.

Supportive Housing Improves Safety for Female Sex Workers: B.C. Study

Canadian Press, (05.09.2012)  Keven Drews

Female sex workers who reside in supportive-housing units feel more control over negotiating condom use and have less trouble with the police than prostitutes working the streets, a new Canadian study found. Researchers from the University of British Columbia and the BC Center for Excellence in HIV/AIDS surveyed 39 FSWs living in Vancouver for the study.

The Atira Women’s Resource Society and the RainCity Housing and Support Society (RHSS) run the FSWs’ housing programs in Downtown Eastside under a harm-reduction model. The FSWs have a place to live and pay rent; what they do in their own units is their business. Security measures include female-only buildings, public surveillance cameras, onsite staffing, and sign-in for guests and clients.

The women reported less exposure to violence and diseases such as HIV when operating from the units, and more power to refuse unwanted services and avoid violent abusers. The FSWs interviewed from July 2009 to March 2010 were ages 22-58, and all reported a history of illegal drug abuse.

Leslie Remund, associate director of RHSS, said that under the program, a Vancouver police liaison makes onsite visits to build relationships with the women. In addition, an onsite advocate helps clients navigate the criminal justice system.

One interviewee who previously had reported feeling “paranoid” about the police said officers now greet her; another said she thought the police were pleased about the unit because it kept the women off the streets.

Caste Locks Nepal’s Sex Workers into Their Profession

*Inter Press Service*, (05.07.2012) Naresh Newar

It would take special effort to empower an “untouchable” Hindu caste in Nepal that has long been associated with entertainment and prostitution, social activists say. Four years ago, the government banned Badis from engaging in sex work, and it promised assistance.

A failure to implement the ban has led some local communities to form monitoring groups backed by violent vigilantes. Many Badi girls and women have been displaced by such a group in the town of Muda. Nonetheless, Badis are not allowed legal businesses.

Riddha Bhandari, a leader of Muda’s monitoring group, said it formed in part to prevent HIV’s spread. “We’re trying to help the Badi women start new dignified lives, but we do admit that there are no viable alternatives,” said Bhandari, advocating government support.

“Most Badis are uneducated and have no farms or livestock,” explained Uma Badi, an activist and one of the few college-educated Badi women. Following Nepal’s 1996-2006 civil war, political instability has continued. “I have met three different prime ministers in the past few years,” Uma said. “They promise support but forget us as soon as we head back to our villages.”

“We didn’t want to continue with prostitution but the government has failed to fulfill its promises of rehabilitation,” said Bishal Nepali, husband of a sex worker. The aid package was to have included housing and work assistance and scholarships for Badi children.

“My family has survived on this trade for generations,” said Sabitri Nepali, 30, in Kailali district. “My mother was a sex worker and I continued the family profession.” “We defyed the ban and continued with our traditional occupation,” said Kalpana Badi. “How could we survive without incomes? Think about our children.”

Study: Stem Cell Therapy Could Be New Weapon in Fight Against HIV

*Voice of America News*, (05.04.2012) Jessica Berman

US researchers are preparing to launch human clinical trials of an approach that uses genetically modified stem cells, master cells that can be altered to become any type of cell, to fight HIV.

Joseph Anderson, a stem cell researcher at the University of California-Davis’ Institute for Regenerative Cures, and colleagues bred mice to have a human immune system, injected them with stem cells genetically modified with a trio of HIV-resistant genes, then infected them with HIV.

The mice were able to block HIV infection and maintain normal immune systems, “even though the virus was still there,” Anderson said. “We were able to still detect virus that was replicating inside of the mice. However, because we put in genetically modified stem cells, the resistant immune cells were able to maintain a normal immune cell’s level and maintain a functional immune system.”

The mice’s immune systems functioned normally, with the HIV-resistant cells thriving and reproducing. Anderson hopes next to advance to clinical trials using genetically modified, HIV-resistant immune cells in HIV-positive human subjects.

The goal would be “to maintain a normal human immune system in patients that have HIV infection. Hopefully, they’ll be able to stop taking the antiretroviral drugs that they normally take, because the genetically resistant stem cells will be able to fight off the virus in the body,” Anderson said.


Most Deaths In Children Under 5 From Preventable Infectious Causes, Study Suggests

"Most deaths of young children around the world are from mainly preventable infectious causes," according to a study published in the Lancet on Friday, *BBC News* reports. A team led by researchers at the Johns Hopkins University Bloomberg School of Public Health looked at mortality figures from 2010 and "found two-thirds of the 7.6 million children who died before their fifth birthday did so due to infectious causes—and pneumonia was found to be the leading cause of death," the news service writes. "They found child deaths had fallen by two million (26 percent) since 2000, and there have been significant reductions in leading causes of death including diarrhea and measles—as well as pneumonia," *BBC* notes (5/11). However, the authors "caution the decline is not sufficient enough" to achieve the fourth Millennium Development Goal, "which seeks to reduce child mortality by two-thirds in 2015," a Johns Hopkins *press release* writes (5/10).
As Agriculture Intensifies To Promote Food Security, Prevention Research For Buruli Ulcer Also Must Intensify

"Buruli ulcer could spread as agriculture intensifies in Africa, making prevention research vital," Rousseau Djouaka, a researcher at the Benin branch of the International Institute for Tropical Agriculture (IITA), argues in this SciDev.Net opinion piece. "The intensification of lowland agriculture has been linked with the increased incidence of human diseases such as malaria, schistosomiasis and Buruli ulcer (BU)," he writes, noting, "Of these, BU remains the least well documented and most neglected in the wet agro-ecosystems of west and central Africa." He provides statistics regarding infection rates in Africa and notes, "People affected by the skin infection, caused by the bacterium Mycobacterium ulcerans, develop large ulcers which often result in scarring, deformities, amputations, and disabilities, especially when the diagnosis is delayed."

"If identified early enough, BU patients can be treated successfully. But one of the missing pieces in our understanding of the disease is how people are exposed to the bacterium — this understanding is vital for taking steps to prevent the infection," Djouaka continues. He highlights the association between BU transmission and changes in land use, discusses the high cost of treatment and funding shortages for combating the disease, and concludes, "Steps are being taken in the right direction," but "a lack of resources is limiting how fast these initiatives can be implemented. At a time when the intensification of agriculture is promoted for food security, we also need to intensify research into preventing BU" (5/11).

Friday, May 11, 2012

A*STAR Scientists Discover ‘Switch’ To Boost Anti-Viral Response To Fight Infectious Diseases

1. Singapore scientists from Bioprocessing Technology Institute (BTI) under the Agency of Science, Technology and Research (A*STAR) have for the first time, identified the molecular ‘switch’ that directly triggers the body’s first line of defence against pathogens, more accurately known as the body’s “innate immunity”. The scientists found that this ‘switch’ called Bruton’s tyrosine kinase (BTK) when turned on, activates the production of interferons — a potent class of virus killers that enables the body to fight harmful pathogens such as dengue and influenza viruses.

2. While there are anti-viral drugs to treat influenza, the high rates of mutation that are characteristic of the influenza[1] virus have made it difficult to treat with one universal drug or vaccine. As for dengue[2], there are currently no clinically approved vaccines or cures either. This discovery of BTK’s role as a critical ‘switch’ that boosts the body’s anti-viral response, paves the way for developing anti-viral drugs that target the BTK ‘switch’ to fight infectious diseases.

3. To investigate the role of BTK in innate immunity, the research team from BTI extracted a class of innate immune cells known as macrophages[3] from both normal mice and from mice deficient in BTK and challenged them with the dengue virus. They found that the BTK-deficient immune cells were unable to produce interferons, and hence had much higher viral counts compared to the healthy immune cells that had high-levels of interferons to fight the virus effectively.

4. To further demonstrate the critical role of BTK in anti-viral response, the team focussed on BTK’s role in Toll-like Receptor 3 (TLR3) signaling. TLR3 is needed for cells to activate the interferon response when cells are infected by viruses. The team examined the effect of having a perpetually-“on” or -“off” BTK ‘switch’ in TLR3 signaling. They uncovered that a constitutively active or ‘on” BTK ‘switch’ enhanced the production of interferon, resulting in a stronger and more lasting anti-viral response with significant reduction in Dengue viral counts. In contrast, a perpetually “off” BTK ‘switch’ led to a poor anti-viral response with very low levels of interferons produced, and little protection against Dengue virus infection.

5. Previously, scientists have always thought that BTK is important primarily in antibody production due to observations made of an inherited genetic disorder in humans called X-linked Agammaglobulinemia (XLA). These patients do not have a functional BTK ‘switch’, and are unable to produce antibodies because defects in BTK cripple maturation of B cells, a type of white blood cell that produces antibodies.

6. “We are very excited because this is the first time that the link between BTK and its critical role in the immediate anti-viral responses of the immune system, triggered in response to invading viruses like Dengue, is definitively demonstrated”, said Dr. Koon-Guan Lee, the first author of this paper.
7. Said Professor Kong-Peng Lam, Acting Executive Director of BTI and the Head of the Immunology Group that conducted the research, “This study adds new insights to the understanding of how the body’s innate immunity is triggered to create an effective immune response. It is a prime example of how better understanding in basic biological systems brings us a step closer to understanding the mechanism of human diseases, and enables us to find more effective treatment strategies to combat deadly viral diseases, which we have yet to find cures for.”

**Pneumonia and Preterm Birth Complications Are the Leading Causes of Childhood Death**

ScienceDaily (May 10, 2012) — Pneumonia is the leading cause of death among children under 5, according to a new study led by researchers at the Johns Hopkins Bloomberg School of Public Health. They examined the distribution of child deaths globally by cause in 2010 and found that 64 percent were attributable to infectious causes and 40 percent occurred in neonates. The authors’ findings, published in the May issue of the *Lancet*, suggest a decline in the total number of deaths between 2000 and 2010, however, they caution the decline is not sufficient enough to reach Millennium Development Goal number 4, which seeks to reduce child mortality by two-thirds in 2015.

"The numbers are staggering," said Robert Black, MD, MPH, senior author of the study and the Edgar Berman Professor and chair in the Bloomberg School’s Department of International Health. "Of 7.6 million deaths globally in children younger than 5, 1.4 million or 18 percent were a result of pneumonia, 1.1 million or 14 percent were related to preterm birth complications and 0.8 million or 11 percent were a result of diarrhea. Despite tremendous efforts to identify relevant data, the causes of only 2.7 percent of deaths in children younger than 5 years were medically certified in 2010. National health systems, as well as registration and medical certification of deaths, need to be promoted and strengthened to enable better accountability for the survival of children."

Researchers updated the total number of deaths in children ages 0-27 days and 1-59 months and applied the deaths by cause to their corresponding country. To calculate the numbers, they used vital registration data for countries with an adequate vital registration system; applied a multinomial logistic regression model to vital registration data for low-mortality countries without adequate vital registration and used a similar multinomial logistic regression with verbal autopsy data for high-mortality countries. To generate regional and global estimates, the team aggregated country results. Researchers found that although the burden of deaths among children younger than 5 decreased by 2 million between 2000 and 2010, continued reduction at this rate would not reduce child mortality by two-thirds between 1990 and 2015 as outlined by the United Nations’ Millennium Development Goal number 4. Among the causes of death that decreased globally, uncommon causes such as tetanus, measles and AIDS dropped at an annual rate sufficient to attain Millennium Development Goal number 4, and in Africa, malaria experienced a similar reduction.

"Pneumonia, measles and diarrhea contributed the most reduction between 2000 and 2010, however, the reduction was not significant enough to achieve Millennium Development Goal number 4," said Li Liu, PhD, MHS, lead author of the study and an assistant scientist with the Bloomberg School’s Department of International Health. "Among the 3 leading causes of death from 2000-2010, diarrhea declined the fastest at 4 percent, followed by pneumonia at 3 percent and preterm birth complications at only 2 percent. Child survival strategies should direct resources toward the leading causes of child mortality, with attention focusing on infectious and neonatal causes."

The authors suggest, "More rapid decreases from 2010-2015 will need accelerated reduction for the most common causes of death, notably pneumonia and preterm birth complications. Continued efforts to gather high-quality data and enhance estimation methods are essential for the improvement of future estimates."

**Journal Reference:**

U.S. sheds the Helms Rule’s legacy

By: J. Lester Feder
May 13, 2012 10:00 PM EDT

This July, a shadow that Jesse Helms cast over HIV policy will be dramatically lifted. The enormous International AIDS Conference will meet in the United States for the first time in more than 20 years, ending a boycott that protested a policy the late North Carolina Republican senator pushed into law.

The “Helms rule” denied U.S. visas to people who are HIV positive. It was lifted in 2009, thanks to efforts by both President Barack Obama; his predecessor, President George W. Bush; and both parties in Congress. The policy was especially painful to advocates because U.S. scientific and financial investments are largely responsible for stemming the tide of the epidemic around the world.

When the meeting convenes in Washington this summer, it will signal that the U.S. has brought its HIV policies into better alignment with the principles it advocates abroad.

But the meeting will also highlight other ways that the U.S. has fallen short, advocates say. Washington has an infection rate that rivals some African countries, symbolizing that domestic efforts have not matched the push to combat AIDS overseas. And, they say, it will highlight Obama’s stamp on U.S. AIDS policy, because it was only after he took office that the country matched its global efforts to fight the disease with a coordinated commitment at home.

In 2010, the Obama administration unveiled the country’s first national HIV/AIDS strategy to focus on high-risk populations, gay men and African-Americans. The administration has also increased domestic funding for HIV treatment and research even as some other public health programs have been cut.

The White House also regards the health reform law as a major HIV intervention for people at risk or living with the virus, said Grant Colfax, director of the Office of National AIDS Policy. He cited free HIV testing, a ban on insurers denying coverage for pre-existing conditions and rules that make it easier for low-income people to get insurance.

This has not been enough for some advocates who are frustrated that key initiatives, like the AIDS Drug Assistance Programs, haven’t kept pace with demand.

AIDS Healthcare Foundation President Michael Weinstein even went so far as to say that “U.S. AIDS programs have been starved under Obama” as part of a messaging campaign leading up to this summer’s conference.

But many are more supportive of Obama, whom they credit with continuing global efforts despite the economic slump while also stepping up domestic efforts.

Yet around 55,000 people become infected with HIV in the United States each year, and that shows no sign of dropping.

“We have, for a first-world country, quite a severe HIV epidemic, and it’s not declining,” said Johns Hopkins University epidemiologist Chris Beyrer, incoming president-elect of the International AIDS Society. But he said Obama’s shift to the domestic crisis “is an important legacy already.”

Anthony Fauci of the National Institutes of Health, a founder of the international conference and public face of the research and prevention efforts since the early years, said he intends to stress that although there has been tremendous progress, much more work needs to be done.

“I’m going to point out that we’re sitting here right in the middle of Washington, D.C.,” said Fauci, who spent years trying to get the Reagan White House to take the disease seriously and is slated to open the conference with a keynote lecture entitled “Ending the HIV Epidemic.”

“Though we’ve made it fall off the radar screen a little bit in this country, we still have a significant problem,” he said.

Special Reports

To give or not to give Namibian prisoners condoms

By AFRICA REVIEW Correspondent in Windhoek Posted Friday, May 11 2012 at 10:58

While the Namibian Government is to be applauded for implementing a comprehensive HIV testing, counselling, prevention and treatment programme for the benefit of the public, a standardised approach to controlling the same in prisons is lacking.

Namibia currently ranks among the top five African countries with the highest per capita rates of imprisonment, with 267 per 100,000 people currently serving sentences in prison or in pre-trial
detention. Interviews reveal a pattern of compromised health, safety and security of inmates and detainees.

In addition, an initiative to distribute condoms amongst Namibian male prison inmates is yet to take shape, more than ten years after it was first discussed in the country’s legislative chambers. The move was meant to reduce the spiralling rate of HIV/Aids in the country’s jails.

The National Strategic Plan on HIV/AIDS which was initiated in 2000 calls for male prisoners to receive condoms – a move that has had some lawmakers and prison officials seething in anger. Early signs indicated that the initiative would not see the light of day, when then President Sam Nujoma failed to launch it as per its time line the same year.

**Homosexuality**

The plan forms part of the Third Medium Term Plan (MTPIII) which stretched over five years (2000-2005) and has guided Namibia’s development plans. The plan, which was discussed by Ministers and Governors, calls on the government to provide the Highly Active Anti-retroviral Therapy (Haart) and the Prevention of Mother-to-Child Transmission (PMTCT) to prison health services for distribution to people meeting the existing inclusion criteria.

The Ministry of Prisons and Correctional Services has always argued that they were not obliged to obey official directives. They demanded to know why the Ministry of Health wanted condoms distributed among inmates as men and women were separated. They also argued that it would promote homosexuality in prisons.

However, the Health Ministry countered that the proposal to provide condoms did not hinge on sexual lust, but was aimed at preventing the spread of HIV/AIDS as gang rapes and sodomy are rife in prisons.

A few weeks ago, the debate on whether condoms should be distributed in Namibian prisons caused a commotion in Parliament, with members of the ruling Swapo party opposing the motion. Opposition members were however having none of it, and were quick to urge their ruling party counterparts to take a reality check.

"Those in the cells have (sexual) needs they want satisfied and men help men and women help women to satisfy these needs," Elma Dienda of the opposition party CoD said, calling on government to reverse its decision not to distribute condoms in prisons.

"This (non-distribution) would spread HIV/AIDS and MPs should not deny such acts take place in prisons," Dienda commented.

All but banging the table, an angry Petrus Ilonga, deputy Labour minister, said he and other Namibians were imprisoned during apartheid but had not practised sodomy.

**Inadequate staffing**

"I and Ben Ulenga (of CoD) and others were on Robben Island Prison in South Africa for many years, but never, I repeat; never did we practise something like that. Distributing condoms to prisoners just encourages them," he argued.

The distribution of condoms in Namibian prisons has had equally mixed responses from the various spheres of Namibian society. For many, the initiative is a positive move to alleviate the scourge of HIV/AIDS behind bars and grant equal access to health services to inmates. But for others, just the mere thought that such an initiative is being considered is enough to have them reeling in disbelief.

The Namibian government reports that at least 12 per cent of the prison population is infected with HIV/AIDS, although the percentage may be much higher due to under-reporting.

A combination of lengthy pre-trial detentions, substandard nutrition and sanitation, violence, rape, consensual unprotected sex and inadequate staffing in prisons contribute to HIV transmission. But the criminalisation of sodomy has resulted in a prohibition on the distribution of condoms in prisons.

The health conditions in Namibia’s prisons are similar to those in detention centres. Former inmates, doctors, NGO representatives and former wardens corroborated stories of daily violence, gang activity, overcrowding, forced and consensual unprotected sex, malnutrition, corruption, and poor health care.

Recently, a male inmate from the Windhoek Central Prison involved in a four-man love affair was stabbed to death when the relationship went sour. It was alleged that one of men could not accept their relationship went bad, after which a fight broke out leading to the death of one.

**Human rights**

In another case reported in the media earlier this year, an inmate appeared in the Gobabis Magistrate’s Court in January on a charge of sodomy. The victim, who was sodomised several times during the evening, reported the matter to the police officer conducting a routine morning visit to the holding cells the following day.
According to a report on HIV/Aids and prisoners’ rights in Namibia titled ‘Struggle to Survive’—compiled by Legal Assistance Centre Aids Law Unit and University of Wyoming College of Law—sex in prisons occur in three ways, one of which is consensual sex when two inmates engage in a voluntary and consensual intimate relationship.

Then there is coercive sex, which occurs when an inmate engages in sexual contact or sexual relationship with another inmate in order to gain a perceived advantage or benefit (for example, submission in return for protection or other favours).

Lastly, there is rape, which occurs when an inmate physically forces him or herself sexually upon another inmate. All three types of sexual encounters can transmit HIV/Aids.

Of great concern is when the inmates are released from custody and are involved in sexual relationships with community members outside prison. Namibia’s national policy on HIV/Aids includes a commitment that all trial-awaiting detainees, prisoners and prison staff have access to the same standard of treatment, care and support available to the general population. But many argue that such policies are only good on paper, as their implementation is almost never carried out.

International human rights laws, which protects the rights of inmates, stipulate that an inmate does not surrender all fundamental human rights upon entering prison. One such law is the United Nations Universal Declaration on Human Rights, which guarantees the right to the highest attainable standard of health for everyone, including prisoners.

June 2012

Criminal Injustice (long)
by Sean Strub with Profiles as Told to Cristina González

HIV criminalization laws do little to stem the epidemic or protect public health. Instead, they often backfire and discourage people from being tested. Here, three courageous advocates share their stories of HIV criminalization and their crusade for health, welfare and justice.

Sometimes HIV stigma is manifest in obvious and laughably insulting ways—such as someone recoiling from an embrace or taking ridiculous measures to sanitize a dish or towel we used. At other times it takes a subtler form—a prejudgment, often masquerading as compassion.

But when people are accused of or prosecuted for not disclosing their HIV status before having sex, they experience stigma in an entirely different dimension. They may find their names and photographs plastered across the local news with hysterical headlines calling them “AIDS predators” or “AIDS monsters,” accompanied by news stories claiming they infected or put others at significant risk, when that is utterly false.

I can’t imagine what it has been like for Nick Rhoades, Monique Moree and Robert Suttle—three brave survivors of HIV criminalization prosecutions who have courageously shared their stories and become activists—or for the thousands of people with HIV around the world charged with “HIV crimes.”

I am proud to work with Nick, Monique and Robert; they are all moving examples of the power of telling the truths about our lives. Last fall I filmed them for HIV Is Not a Crime, a short documentary about criminalization. The film has personalized the issue for thousands, and Nick, Monique and Robert have become public spokespeople, combating stigma and criminalization.

Rather than being publicly shamed and ridiculed, they should be celebrated and admired for how they have transformed a cruelly unjust and difficult episode in their lives into service that is helping others.

Nick now works from his home in Iowa for the Positive Justice Project, a collaboration of more than 40 policy professionals and experts working to repeal HIV-specific criminal statutes. Monique opened a testing and support drop-in center in her hometown, Holly Hills, South Carolina, where her father is a well-known pastor. She also speaks to community groups about her experience. Robert moved from Shreveport, Louisiana, to the Northeast to work with me at SERO (theseroproject.org), documenting and raising awareness of HIV criminalization and providing support to those charged or at risk of being prosecuted.

Several years ago, when criminalization became the focus of my advocacy work, many people viewed the issue as a civil rights violation, one on a long list of injustices in the criminal justice system. It is that, for sure. But it is also a serious public health concern, as the best defense against prosecution is ignorance of one’s HIV status. Criminalization discourages HIV testing, punishing those who know their status, conveying the chilling message, “Take the test and risk arrest.”

Criminalization is inherently discriminatory; the approximately 35 states with HIV-specific statutes don’t have statutes addressing hepatitis, HPV or other sexually transmitted pathogens that, if left
untreated, can kill people. That’s because those viruses aren’t associated with outlaw sexualities, gay men, anal intercourse, people of color or people who use drugs.

The public’s appetite for beating up people with HIV remains enormous, even among communities thought to be educated about HIV/AIDS. Researchers at the University of Minnesota found that 63 percent of gay men (including up to 79 percent of very young gay men) and even 38 percent of HIV-positive gay men support HIV-specific criminal laws.

When people examine the issue more closely, those numbers change. Almost everyone will agree that sentencing in many of these cases is vastly disproportionate to any actual or potential harm. Most people will understand why HIV-specific criminal statutes—literally creating a different set of laws for people with HIV—are wrong, just as creating different laws for people based on their skin color, gender or sexual orientation is wrong. The tough question concerns the appropriate role, if any, for criminal law in the context of harmful sexually transmitted pathogens. Such laws should focus on the intent to harm, the actual risk created, if any, and the actual damage inflicted—if any.

I am optimistic that we will ultimately win this battle. But it will be a long and difficult struggle, and it may well get worse before it gets better. Last year, Nebraska made it a felony for people with HIV to sneeze or vomit in the direction of a law enforcement officer; legislators in Maryland recently tried to increase their nondisclosure penalty from three to 25 years. Fortunately, there are also signs of hope, including growing advocacy at a local level: People with HIV and their allies in Iowa recently had a bill introduced in their legislature to dramatically improve that state’s draconian statute.

But the most promising signs of hope are found in people like Nick, Monique and Robert, who are, in the best of the self-empowerment tradition, fighting back. I salute them, and I think you will too, when you read their accounts of experiencing HIV criminalization. Their voices will stay with you and, I hope, inspire you to join the battle for justice for people living with HIV.

Sean Strub is executive director of SERO (theseroproject.org). He cofounded the Positive Justice Project and is the founder of and advisory editor of POZ magazine. He has had HIV for more than 30 years.

**Robert Suttle, 33, Milford, Pennsylvania**

After a brief and contentious relationship ended, Robert Suttle’s former partner reported him to the police, causing Suttle to be charged under Louisiana’s “Intentional Exposure to AIDS Virus” criminal statute. Little was done to investigate the charges, and Suttle was never accused of transmitting HIV. After serving six months in prison, Suttle emerged with a newfound purpose and goal: to abolish HIV criminalization laws in the United States and around the globe.

There it was on the kitchen counter: a search warrant. I came home from work one day in late summer 2008, juggling bags, keys and phone—and spotted it. Someone had been in my apartment. They had gone through my things, opened drawers and closets, rifled through documents and prescription bottles. They were looking for anything related to HIV.

It began on New Year’s Eve 2007, when I met someone through a mutual friend. We had a casual relationship. It was short and contentious. When I stopped seeing him, he kept threatening to press charges for not having initially disclosed my HIV status, and that’s exactly what he did.

Months later, there was that search warrant. Then in August, the police arrested me at work. Everything hit the fan. I wasn’t out about my sexuality and had not disclosed my HIV status to my family. Everything was private—my diagnosis, my relationships. But now, everyone knew I had HIV, and people drew their own conclusions about my sexuality.

Since my diagnosis, I had learned about HIV and how to live day to day. I didn’t feel I needed to justify anything to anyone. But I was vulnerable. Now [with my arrest], things I’d kept private were made known. I was exposed.

I spent the next two years in and out of court until I was sentenced in June 2010: ordered to serve six months in prison, and given a 15-year sex offender status. Underneath the photograph on my Louisiana driver’s license, in big red capital letters, it says “SEX OFFENDER.” I never thought this would happen to
me. I'd gone to school, earned a degree, tried to make something good out of myself. Now all that was over, and it was devastating. I didn't know what this would lead to, but I knew what a conviction meant in the state of Louisiana, in the South. Along with being black, being gay and being HIV positive, I would now be a convicted felon and a registered sex offender.

While in jail, I thought about my life, because I knew I needed a new plan. The day after my release, I went online and started researching and finally found a name for what I was experiencing: criminalization. I found Sean Strub's phone number on something he had written about fighting HIV criminalization and called it within 48 hours of my release from prison. I told Sean I wanted to help, that this was what I was prepared to devote my life to—abolishing HIV criminalization laws.

Since then I've traveled to Geneva and Oslo speaking to UNAIDS about my story. I've moved to Pennsylvania to work with Sean Strub launching SERO, a nonprofit initiative combating HIV criminalization, stigma and discrimination and promoting the empowerment of people with HIV.

The courts and the lawyers do not understand HIV or the science of transmission. HIV is not a crime. Criminalization laws are not prevention. In Louisiana, they're just another way to lock up young black men.

Today, I stand as a voice for people who will not or cannot speak for themselves. I am speaking for all people who don't have the strength.

**Nick Rhoades, 37, Waverly, Iowa**

Nick Rhoades is HIV positive. He had sex. He had an undetectable viral load. He used a condom. For this, he learned, he could be going to jail for a very long time. After the one-time partner pressed charges, Rhoades received the maximum sentence: 25 years in prison and lifetime sex offender status. Letters from advocates got the judge to reconsider the sentence. Rhoades was released after about a year, but he still has sex offender registration requirements that are nothing short of medieval in their cruelty, and his life has been forever changed.

In 2007, I was working at a video store, taking time out to get my life together. I had just moved back home, close to my family. I was finding the right kind of support and the right kind of HIV treatment. For the first time ever, I was starting to feel hopeful about my future. And then three armed police detectives approached me at my place of business and asked me to accompany them to the police station.

I had had a one-time encounter with a guy I had met online. A week or so later, a warrant had been issued to arrest me for “criminal transmission of HIV.” The fact that transmission of HIV did not actually occur didn’t matter. I was looking at a Class B felony, with a 25-year prison sentence. I was 33 years old.

As I sat in the police interrogation room revealing personal, invasive details, I didn’t think I could survive what I knew would be a hellish experience. I was scared. It was the last straw. I lost my desire to live.

The headline in the local newspaper read, “[Local] Man Arrested for Transmitting HIV.” For close to a year, my life consisted of a seven-week stay at an acute psychiatric care facility and nine months in a maximum-security county jail (six weeks in solitary confinement). I never saw a clock; I never looked out a window.

Finally, I had my day in court. My attorney advised me to plead guilty, and we hoped for a plea bargain from the prosecutor. I entered my plea and was sentenced then and there. The court had conducted a presentencing investigation just one day earlier, and the results were reviewed with me in a small office near the courtroom, five minutes before I went back into court in my shackles, handcuffs and orange jumpsuit.

Sentencing was swift. The judge pronounced me guilty and sentenced me to the maximum, 25 years in prison, with lifetime sex offender registration.

I'm HIV positive. I had sex. I used a condom. No transmission of HIV occurred. My viral load was undetectable. This man—my accuser—chose to have sex with me, and we had safe sex.

But none of this mattered.
Later I was sent back to court. Multiple letters on my behalf, from advocates all over the world, as well as family and friends, had been sent to the judge, and my sentence was reconsidered. I was released. That night was the first time in months that I slept in serene darkness—no cameras, no guards—in a place I called home. It felt unreal.

I was considered likely to re-offend, and I was classified in the highest risk category. This requires me to register with authorities every three months. I cannot be around minors, even family members, without their parents’ supervision. All my computers, text and phone records—and those of anyone living in my home—can be confiscated at any time. I am not allowed to have casual sex, watch pornography or use social networking sites. I may not leave my county without permission or the state without a travel permit. I have a midnight curfew. I may not have liquor in my home or visit a bar. I must take an invasive polygraph test every six months and visit my probation officer every two weeks. I was even threatened with “phalometric testing,” which I think involves attaching some device to my penis to measure my sexual response to different stimuli.

My life is forever marked by one night. One night and one outdated law.

But my life is now full of advocacy and volunteer work. I worked in Iowa to revitalize HIV support group systems, and I have met with legislators, sharing my story and my experience. I’ve traveled to Geneva to speak to U.N. agencies; I’m on the advisory board of SERO, and I work for the Center for HIV Law & Policy’s Positive Justice Project.

Why? Because laws should promote public health and protect human rights. And clear evidence shows that HIV criminalization laws do neither of those things.

**Monique Moree, 30, Summerville, South Carolina**

_A few months after testing positive, and after a brief hookup with a fellow officer, Monique Moree found herself facing an Army court on a charge of sexual assault. Following a humiliating trial, Moree was discharged from the U.S. Army. But she is on a new mission: letting the world know that HIV is not a crime._

I was stationed at Fort Jackson, South Carolina, serving out my Army contract. My parents lived nearby. I had two children and was pregnant with my third and in the middle of a divorce. It was a Friday morning, and I was at my parent’s house when I got the first call.

A routine pregnancy blood test had showed I was HIV positive. I thought I was hearing things. I was confused. Surely, this nurse had me mixed up with someone else. I didn’t suspect I was positive. I was in the service and got tested regularly. I was just recently married—we had not yet celebrated our one-year anniversary. I had not engaged in any risk behaviors I thought would result in HIV.

I went to the clinic, and the nurse showed me the test result. I looked at her with a blank stare. I was tested again. Again, it came back positive. After that second test, I knew this was serious.

I tried to move on and live as best I could, but I was scared. I didn’t know what the Army would do with me, but I knew I needed treatment; I needed help. So I marched into my supervisor’s office and told her, because I thought I had to. I didn’t.

I got the treatment I needed, and I felt supported by my family and my colleagues. I had an HIV-negative baby, and I started living my life.

Months later, I met a fellow soldier. I decided to let him take me out.

One thing led to another, but I couldn’t tell him I was HIV positive, so I just told him he needed to use a condom. He didn’t want to.

Five months later, I got the second phone call, a suspicious one from my supervisor—so many personal questions. At the end of that call, I was told to report to base. When I got there, I was immediately arrested and charged with sexual assault.

My children were taken from me and put into my parent’s custody. I was moved out of family housing and into barracks. I was watched and accompanied everywhere for five months of trial.

This was a dark time. I didn’t know what I could do, should do. There was only one thought recurring in my mind: “I don’t care about my life anymore.”
The trial was humiliating. The court and the prosecutors asked intimate details and stopped numerous times to look into the science about HIV. But then, the charges were dropped.

My partner’s testimony saved me. He asked them to let me go. He said he was responsible for his own actions and confirmed that I told him he needed to wear a condom. I wasn’t convicted, but I was discharged from the U.S. Army. But I wasn’t free.

I spent the next two years in and out of psychiatric wards, trying to understand what had happened, trying to find my voice. In 2010, after my last hospital stay, I went to my father’s church. I was sick of being silent. So I opened my mouth and told my entire church. I stopped the service and said, “I need your prayers. I’m HIV positive.”

And then I immediately looked for a rock to hide under. But instead, there were so many hugs. So many tears. There was support. There was understanding. And I realized I had to come forth to help other people live their lives too.

Now I’ve participated in conferences and radio shows. I am in HIV Is Not a Crime and was featured in an In the Life television program on HIV criminalization. I’m on the advisory board of SERO. I wrote a book, and last year I opened Monique’s Hope for a Cure Outreach Services, a treatment center in a rural community in South Carolina. I want people to get educated, to get the services they need and to break down stigma.

Criminalization laws only make it harder for people trying to live with HIV. I want people to know that HIV is not a crime.

Third Of World Carrying TB; Disease Could Become Incurable Without Action, WHO Warns

"A third of the world’s population is carrying tuberculosis [TB], and the disease could become incurable if governments fail to act, the World Health Organization (WHO) has warned," noting that a "[l]ack of funding for public health programs, the sale of inaccurate blood tests and the misuse of drugs, particularly in the private health sector, are hampering the fight against the disease and leading to drug resistance," the Independent reports. "The rate of TB deaths had declined dramatically—by 40 percent between 1990 and 2000—after a worldwide health campaign, which was particularly successful in China," but "the emergence of drug-resistant strains threatens to halt progress and jeopardizes the WHO’s goal of eradicating the disease as a public health problem by 2050," the newspaper writes, noting, "Two billion people are carriers of the TB bacillus" globally.

"Mario Raviglione, director of the WHO's Stop TB campaign, said: 'What we are seeing worldwide is the emergence of strains of the bacillus causing tuberculosis that are resistant to most of the drugs we have available,'" the newspaper notes. "Extreme drug-resistant strains of TB have now been found in 70 countries"; "doctors in India reported four patients this year who did not respond to any drugs at all"; and "doctors in Iran and Italy have also found patients who are apparently resistant to all drugs," according to the Independent, which provides statistics on TB infection and death rates, discusses the reasons behind the emergence of drug-resistant strains. "Drug resistance has increased the cost of combating TB worldwide because additional, more expensive, medicines are needed. But international aid has dried up," according to the newspaper (Livingstone, 5/14).

Cell Biology: How Ribosomes Override Their Blockades

ScienceDaily (May 14, 2012) — Ribosomes are "protein factories" in the cells of all living things. They produce proteins based on existing genetic codes stored on special nucleic acid molecules. These molecules, also called messenger RNA (mRNA) due to the genetic information encoded on them, are read by ribosomes in a stepwise manner. Defined start and stop signals on the mRNA direct this process. If a stop signal is missing, protein formation cannot be completed and the ribosome's mode of operation is blocked.

Until now, it was not understood in all details how a ribosome can overcome such a blockade. At the center of this repair process, called Trans-Translation, is an additional nucleic acid molecule (tmRNA) that unites characteristics of mRNA and another nucleic acid molecule, the transferRNA (tRNA). The tRNA transfers the correct amino acids to the respective gene sequence on the mRNA during protein biosynthesis. The tmRNA molecule is thus able to smuggle in the missing stop signal and lift the blockade. It was never exactly clear how this large tmRNA molecule moves through the ribosome and smuggles its information into the ribosome's mRNA channel.
This process could now be documented for the first time using cryo-electron microscopy. This method offers the opportunity to examine the spatial and chronological interaction between individual components of macromolecules. This is done by flash-freezing ribosomes in liquid ethane at \(-192\)° Celsius and several hundred-thousand two-dimensional images are projected back into a three-dimensional reconstruction. "With the help of cryo-electron microscopy a unique glimpse of a central key step of the interaction between ribosome, tmRNA, a special protein (SmbP) and the elongation factor G could be attained," explained David Ramrath, doctoral candidate at the Institute for Medical Physics and Biophysics at Charité and primary author of the study.

The mRNA channel, in which the tmRNA must smuggle the missing information, goes straight through the ribosome's middle, between the so-called head and body domains of the small ribosomal subunit. Structural analysis showed that cooperation between ribosome and tmRNA in the event of necessary repair is only possible through a change in conformation, that is a short-term and unexpectedly large swivel movement of the ribosome's head domain.

Journal Reference:

FDA Panel Recommends Gilead's Quad for HIV

Reuters, (05.11.2012) David Morgan
A Food and Drug Administration advisory panel on Friday voted 13-1 to recommend Gilead Sciences Inc.’s Quad pill for people with HIV who have never been treated. However, the independent experts said patients taking the drug should be monitored for possible kidney problems, and they urged more research to assess the safety of Quad for women, who were under-represented in clinical trials.

The panel’s sole “no” voter said data on potential kidney problems and on women’s health were too limited to justify approval. “There are plenty of alternatives to Quad,” said Dr. Michelle Estrella of Johns Hopkins University School of Medicine. “There’s no huge hurry in approving this drug before the outstanding studies are completed.”

The pill is a combination of four agents: an experimental integrase inhibitor (elvitegravir), a booster (cobicistat), and two nucleotide reverse transcriptase inhibitors (emtricitabine and tenofovir).

In clinical trials, Quad was 88 percent effective in suppressing HIV, besting Gilead HIV treatment Atripla’s efficacy of 84 percent. Nonetheless, trial data suggest there were a disproportionate number of kidney problems.

The once-daily pill schedule would help patients adhere to Quad, boosting treatment efficacy, said Gilead. The firm said it has not set a possible price for Quad. In an era of restricted public assistance for treatment, AIDS advocates worry about the cost of new AIDS drugs that offer only modest improvements in treatment.

The panel’s recommendation will be taken up by FDA regulators, and a decision on final approval is expected August 27.

Tennessee Governor Signs Controversial 'Gateway Sexual Activity' Bill

Reuters, (05.11.2012) Tim Ghianni
Gov. Bill Haslam's office confirmed Friday he has signed a bill that prohibits sex education instructors from discussing “gateway sexual activities.” Teachers or outside speakers could face fines of up to $500 for promoting or condoning the touching of “gateway body parts,” including the genitals, buttocks, breasts, and inner thigh.

The bill passed the Senate 28-1 and the House 68-23, but its critics—including the state teachers’ union and Planned Parenthood of Middle and East Tennessee—say it is too vague. They worry that discussion of sexual behaviors could be viewed as an endorsement. “The very ambiguous language in this bill certainly puts teachers in a very difficult situation,” said Tennessee Education Association spokesperson Jerry Winters.

But supporters believe the new law will help better define the state’s abstinence-only sex education policy. David Fowler, president of the Family Action Council of Tennessee, which pushed the measure, said action was needed because some teachers had been instructing about alternative ways to achieve sexual satisfaction without risking pregnancy. He cited an incident at a Nashville high school where a teacher was encouraging girls to perform oral sex on boys in order to apply a condom.
Further, Fowler pointed to a website for a Planned Parenthood-sponsored program at a Knoxville school “that actually lists as possible methods of birth control things like oral sex and anal sex play that I think most Tennesseans would find inappropriate.” The bill does not ban discussions of kissing or holding hands, he said.

N. Korean Leader Grappling with STDs

*Korea Times (Seoul)*, (05.09.2012) Kim Young-jin
A booming prostitution trade may be contributing to a growing number of STD cases in North Korea, an online publication monitoring the impoverished country reports. According to News Focus, the regime had directed Pyongyang’s dermatology hospital to expand its capacity to treat STD patients.

The emergence of a market system has created a newly wealthy demographic in North Korea. Recent visitors to the secretive state have noted that restaurants, massage parlors, and bathhouses run or sanctioned by party officials are popping up in Pyongyang. During the famine of the 1990s, some North Koreans turned to sex work as a way to earn cash.

Meanwhile, Radio Free Asia reports that gonorrhea and other conditions could be spreading through sex between female soldiers and government officials. Citing a source working for a US non-governmental group, RFA said more generals have been requesting penicillin to treat the STD.

Last year, reports emerged that health authorities in North Korea were dealing with the spread of syphilis. Local officials were directed to administer examinations and treatments in response.

Violence Linked to Risky Sexual Behavior

*United Press International*, (05.09.2012)
A new study finds that women who witness crimes in their neighborhood or are victims of abuse are more likely to participate in risky sexual behavior.

Jennifer Walsh, of the Miriam Hospital's Centers for Behavioral and Preventive Medicine in Providence, R.I., and colleagues surveyed 481 women presenting at an urban STD clinic. Most participants were African-American and disadvantaged socioeconomically. The women were assessed for a previous history of violence as well as current sexual risk behaviors.

Compared to the general population, the women in the study reported higher rates of exposure to violence. The team identified four groups of women with differing experiences of violence: 39 percent reported low exposure to violence; 20 percent were chiefly exposed to community violence; 23 were mainly exposed to childhood mistreatment; and 18 percent experienced multiple forms of violence.

The authors found that those women who reported experiencing multiple forms of violence and those who said they were exposed to violence in the community had the highest levels of exposure to sexual risk, including drug and alcohol use before sex, and lifetime number of partners.

[PU editor’s note: The study, “Exposure to Different Types of Violence and Subsequent Sexual Risk Behavior Among Female Sexually Transmitted Disease Clinic Patients: A Latent Class Analysis,” was published in Psychology of Violence (03.19.12;doi:10.1037/a0027716).]

To Fight HIV, Indian Health Workers Say Homosexuality Must Be Legal

by Christopher Werth

It's just after nightfall as Anandrag Davinder, an outreach worker among Mumbai’s mostly hidden community of gay men, wanders down a dark alley beside a busy railway station in Mumbai. His stop is a squalid row of urinal buildings where gay men go to meet, hidden from public view. The stench inside is overwhelming.

"This is a loo. This is a cruising center," Davinder says, stepping into the crowded, nearly pitch-black room. "All the gays are standing here only and saying, 'I like these guys. I want to do sex with this person.' The men here are among what Davinder calls India’s "key population" — those most at risk of contracting HIV. He and his colleague, Husefa Saigoonwala, come here every week to pass out handfuls of condoms.

Davinder and Saigoonwala are with the Humsafar Trust, which provides free HIV tests and other health services to Mumbai's gay community. Its CEO, Vivek Anand, says the reach of organizations like this has increased tenfold in just the past three years thanks in part to a 2009 benchmark ruling in Delhi's High Court.

The ruling struck down a 148-year-old law known as Section 377, a holdover from British colonial rule that made homosexual acts illegal. Many former British colonies still have Section 377 laws. And Anand says that under the legislation, gay men and women were largely ignored by India’s efforts to tackle HIV/AIDS in the country.
Anandrag Davinder is an outreach worker in India. He works with Humsafar Trust, a group that provides free HIV tests and other health services to Mumbai's gay community.

"Three years ago, we were providing services to 30,000 [people]. Three years later, we are providing services to 300,000," says Anand. "That wouldn't have been possible had the Delhi High Court judgment not been in place."

He says that wider level of outreach has allowed health workers to more accurately measure HIV among India's gay population. "That's the idea, that more and more people come out so that we know what is the exact number of HIV positive people in the community," he says.

The government estimates that 7 percent of gay and bisexual Indian men have HIV, compared with less than 1 percent in India as a whole.

A handful of religious leaders and conservative groups are using those figures to argue that homosexuals are fueling a rise of HIV in India. They argue that homosexuality doesn't have a place in Indian culture, and they're petitioning India's Supreme Court to overturn the Delhi High Court ruling.

Efforts to reach several of those groups for this story were unsuccessful. But members of India's government have, at times, expressed similar views. Speaking at an AIDS conference in Delhi last year, India's health minister, Ghulam Nabi Azad, referred to homosexuality as a disease.

"Unfortunately this disease, where a man has a sex with another man — found more in the developed world — has spread in our country," Azad said. "Gay sex is completely unnatural. It should not exist, but it does."

The minister later played down those comments. And earlier this year, the Indian government reversed its position before the Supreme Court. It now says it supports legalizing homosexuality and abolishing Section 377. India's Supreme Court began a six-week-long recess Monday without ruling on the landmark case, which has captivated many in the country. It could decide the case when it returns to session in July.

However, Anand of the Humsafar Trust warns that even if the court upholds the ruling that homosexuality is legal, gay men and women in India still face widespread discrimination by police and health care providers. He points to the death of an HIV-positive team member last year after a hospital initially refused to give him advanced treatment for HIV because of his sexual orientation.

"I was totally ashamed of myself and guilt-ridden that my boy died," Anand says. "My boy died because his second-line treatment was delayed. If this is happening to my team, with all our resources and all our work behind us, you can imagine what must be the situation outside."

He says changing the law is one thing. Changing minds is a whole other challenge.

Christopher Werth reported from India with the help of the International Reporting Project in Washington, D.C.

Sanders plan to lower HIV drug cost
By: J. Lester Feder
May 14, 2012 11:45 PM EDT
Why do American patients pay tens of thousands of dollars each year for HIV drugs that cost just hundreds in Africa?

Drugmakers wave their patent rights in developing countries as part of the President’s Emergency Fund for AIDS Relief. But the higher cost of brand-name drugs in the United States makes it difficult for many HIV patients to stay on drug regimens that can cost as much as $30,000 a year.

That's the challenge a Senate subcommittee will explore on Tuesday at a hearing on how to narrow the gap. It's mainly a vehicle one proposed solution — a proposal by Sen. Bernie Sanders (I-Vt.) that would award prize money rather than grant patent rights to manufacturers that develop new HIV drugs, allowing the medication to go straight to the generic market. But the hearing will also look at the root causes of a dilemma that has had some HIV patients and drugmakers at odds for years.

The challenge for uninsured HIV patients has worsened during the recession, as many states have taken steps to contain costs in the AIDS Drug Assistance Programs funded jointly by state and federal dollars. Many patient advocates are hopeful that the health reform law will get coverage to many low-income HIV patients if it goes into effect in 2014, but they worry that patients could still face high co-pays for specialty drugs and other gaps in coverage.

"These costs can be a huge barrier to treatment," said Mark Harrington, executive director of the Treatment Action Group, citing Centers for Disease Control and Prevention statistics that show 64 percent of people with HIV are going without treatment. This treatment gap not only could cost them their lives, advocates said, but make them more likely to infect others.
Drugmakers contend that they can bring these life-saving drugs to market only if they can make a profit by holding onto their patents. Profits in the developed world also enable them to forgo profits in developing nations, they argue.

“It’s expensive to come up with these medicines and we need to recover the costs,” said Mark Grayson, a spokesman for the Pharmaceutical Research and Manufacturers of America.

Additionally, Grayson said, ADAP and patient assistance programs run by the drug companies provide a lot of help to American patients who need it.

“There shouldn’t be an access problem here in the United States,” Grayson said.

But there are serious gaps in these assistance programs, experts say. As of April 2012, 10 states had waiting lists for their ADAP program, and 15 had taken other cost-containment steps, according to numbers compiled by the National Alliance of State and Territorial AIDS Directors.

And despite the fact that drugmakers offered discount pricing to ADAP programs worth $1.2 billion between 2003 and 2010, it still costs an average of around $10,000 to cover drugs for one patient each year in the program, according to Ann Lefert, the alliance's director of policy and health care access.

Sanders will chair Tuesday's hearing of the Primary Health and Aging Subcommittee of the Health, Education, Labor and Pensions Committee, at which he will push legislation to create a $3 billion fund to offer a prize to developers of new medications in exchange for allowing their products to immediately enter the generic market.

“We should reward innovators for developing these new medicines in a way that does not force any of those who need the drug to wait, suffer and in some cases die just so that the drug developer has time to make its profit,” Sanders said in a statement.

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**School rejects HIV boy’s siblings**

By Matthew Backhouse

5:58 PM Tuesday May 15, 2012

A primary school asked the parents of a four-year-old Whangarei boy with HIV to keep his two older siblings at home for their own safety after other parents came forward with concerns.

The incident follows the boy's alleged exclusion from the Mokopuna childcare centre after parents of other children were told of his condition last week.

The four-year-old boy is due to start at Whau Valley Primary, where the childcare centre is also located, in July.

Principal Robert Clarke said some 20 parents approached him to discuss the issue last Wednesday after the childcare centre held a meeting to discuss the child's HIV status.

Most parents were happy when he told them the school would develop a care plan with the family and stakeholders, but there were two parents who made him "feel uneasy".

Mr Clarke said no threats were made but he was uncomfortable with the questions he was asked. He declined to say what those parents had said.

Mr Clarke then contacted the four-year-old boy's parents to ask them to take home the boy's two siblings, who currently attend the primary school.

"I made the professional call that in the environment of uncertainty, possibly ignorance, I'd go and approach the family and say, 'In the physical and emotional interests and safety of your children, would you mind taking them for a few days'?," he said.

"I went and saw the family straight away, and they were happy with my explanation until I could have further conversations with some people."

The boy's siblings were taken home that day.

Mr Clarke had since spoken to the two parents and was satisfied the situation was cleared up.

The boy's siblings returned to school as usual today.

Mr Clarke said he yesterday held a meeting with three generations of the boy's family, Ministry of Education officials, health officials and a delegation from the New Zealand Aids Foundation.

The school called the meeting to develop a care plan for when the boy starts school in July.

"I was happy to have everybody in there to say, 'The experience you got over there [at the daycare centre] is not what you're going to get here'," Mr Clarke said.

A Ministry of Education spokesman told the Northern Advocate the principal was "reminded" that all primary and secondary schools were required to admit pupils regardless of their medical condition unless a notifiable disease had been confirmed.
"Families of children with HIV are not required to disclose to schools and Early Childhood Education services of their diagnosis as there is no risk posed to other children. HIV is not a notifiable disease," the spokesman said.

Mr Clarke said the school was not reminded of its legal requirements and did not need to be. "I had nobody come to me from the ministry to remind me of my legal requirements because I know the legal requirements."

The boy had been attending the Mokopuna childcare centre for four months before the centre learned he had HIV and asked his mother to keep him at home until a care plan was completed.

Centre management said the boy had not been excluded or expelled. He was welcome to return to the centre once the plan had been created to address his medical needs, centre operator He Puna Marama Trust chief executive Raewyn Tipene said.

However, the Aids Foundation has disputed this, labelling the care plan a strategy to shut out the boy. The trust is now preparing to take legal action over "untrue" claims made by the Aids Foundation, which Ms Tipene said were an attempt to boost its funding.

**HHS Accepts Abstinence-Only Curriculum**

The Department of Health and Human Services has added an abstinence-only sex education curriculum to the range of evidence-based teen pregnancy prevention programs funded by the Obama administration. The Office of Adolescent Health in April added the Heritage Keepers Abstinence Education (HKAE) program to the list, making it eligible for support under the $75 million Teen Pregnancy Prevention Fund.

"What we’re hoping is that getting one program on the list shows they’re willing to look at the issue of teens and sexual risk avoidance," said Valerie Huber, president of the National Abstinence Education Association. "I certainly do hope this could be the beginning of a new trend."

The 2012 federal budget retained $55 million for abstinence-only programs, just a third of the $176 million available the last year President George W. Bush was in office. Several liberal groups signed an April 30 letter asking HHS to explain including HKAE among evidence-based programs.

HKAE met two benchmarks for approval as being evidence-based, said Mark Weber, an HHS spokesperson. It had a robust study design and a statistically significant effect on students’ behavior.

In support of HKAE, HHS cited a 2011 comparative study involving 2,215 middle-school students. Sexual activity among students who did not participate in HKAE rose from 29.2 percent at baseline to 43.2 percent one year after HKAE concluded. It increased less among HKAE participants, from 29.1 percent reporting being sexually active at the beginning to 33.7 percent one year after the program.

**Botswana Makes New Pitch for Circumcision in AIDS Fight**
*Agence France Presse*, (05.14.2012)

A government campaign to thwart the spread of HIV by circumcising nearly half a million Botswana males has managed to reach just 7 percent since it began three years ago.

Other southern African countries also have launched national male circumcision campaigns, including Lesotho, Swaziland, Zambia, and Zimbabwe; all are well below their targets.

There is no tradition of male circumcision in Botswana. Though the procedure is performed with local anesthetic, takes only a few minutes, and has a recovery period of just a few days, fears persist.

"The greatest challenge that we have is the fear of pain amongst men, hence we are having a low turn-out," said Conrad Ntsuape, the effort’s coordinator. "Most men seem to think the pain from the procedure might take long to heal and force them to stay away from school or work for long, but we are still intensifying our education campaign."

Alan Whiteside of the University of KwaZulu-Natal in South Africa said uptake is lagging in many countries across the region. "The problem is not so much that people don’t want to embrace circumcision, it is because sometimes the programs are implemented without the necessary ground work and community participation," the health economist said.

In response, Botswana is launching new advertisements promoting “safe male circumcision” as a lifeline and enlisting the support of popular musicians.
Global Burden of Cancers Attributable to Infections in 2008: A Review and Synthetic Analysis

Lancet Oncology doi:10.1016/S1470-2045(12)70137-7, (05.09.2012) Catherine de Martel, MD; and others

In the current study, Martel and colleagues estimated the respective contribution of infections identified as strong risk factors for specific cancers to the global burden of cancer.

The authors considered viruses, bacteria, and parasites classified as carcinogenic to humans by the International Agency for Research on Cancer. Using estimated cancer incidence data for 2008, the study calculated the infectious agents’ population attributable fraction (PAF) globally and in eight regions. When associations were strong, estimates were based on the prevalence of infection in cancer cases, rather than in the general population. The study extracted estimates for infection prevalence and relative risk from published data.

Of the 12.7 million new cancer cases in 2008, the PAF for infectious agents was 16.1 percent, for about 2 million new cancer cases attributable to infections. The PAF was higher in less developed countries (22.9 percent) than in more developed countries (7.4 percent), ranging from 3.3 percent in Australia and New Zealand to 32.7 percent in sub-Saharan Africa.

Human papillomavirus (HPV), hepatitis B and C viruses, and Helicobacter pylori accounted for 1.9 million cancer cases, mainly cervix uteri, liver, and gastric cancers. Cervix uteri cancers represented about half of infection-related cancers in women; for men, liver and gastric cancers accounted for over 80 percent. About 30 percent of cancers in people below age 50 were attributable to infection.

“Around 2 million cancer cases each year are caused by infectious agents,” the team concluded.

“Application of existing public health methods for infection prevention, such as vaccination, safer injection practice, or antimicrobial treatments, could have a substantial effect on the future burden of cancer worldwide.”

US HIV Aid Has Prevented 741,000 Deaths: Study

Reuters, (05.16.2012) Genevra Pittman

Some 741,000 deaths from any cause were averted in 12 African countries receiving aid from the US President’s Emergency Plan for AIDS Relief, a new study suggests. Previous research has shown PEPFAR-associated declines in AIDS, but it was unclear whether there were any changes in mortality for other illnesses, researchers said.

“There were concerns that there’s been this shift in physicians and nurses [toward HIV clinics] to the detriment of other public health concerns,” said lead author Dr. Eran Bendavid, an infectious-diseases specialist from Stanford University. “We can’t find evidence of unintended harms, or benefits. More or less we find that PEPFAR seems to have been very effective at reducing deaths, probably mostly HIV-specific deaths.”

The study found that in 2003, the year PEPFAR was created, eight to nine deaths occurred per 1,000 adults in 27 African countries, which included nine PEPFAR recipients. By 2008, deaths had declined to four of every 1,000 adults in PEPFAR countries and seven in 1,000 for non-PEPFAR countries. Data were based on surveys of adult women who were asked about recent deaths in their families.

Critics said the more than $20 billion spent on PEPFAR during 2003-2008 could have been spent more wisely, such as on preventing pneumonia and diarrhea.

“No one says that HIV [funding] isn’t making a big difference; the question is whether other things would make an even bigger difference,” said Dr. Ezekiel Emanuel, a medical ethicist from the University of Pennsylvania-Philadelphia. “You cannot escape the ‘How do we allocate the money?’ question when we don’t have enough.”


Vanderbilt researchers find common antibiotic carries heart risk

Vanderbilt researchers have discovered a rare, but important risk posed by the antibiotic azithromycin, commonly called a "Z-pack." The study found a 2.5-fold higher risk of death from cardiovascular death in the first five days of taking azithromycin when compared with another common antibiotic or no antibiotics at all.

Azithromycin, commonly called a “Z-pack” is one of the most popular treatments for bacterial sinus infections and bronchitis. Although it was previously considered to carry little to no cardiac risk, the researchers noted well-documented reports in the published literature as FDA database reports linking azithromycin with serious arrhythmias. Based on this evidence, the Vanderbilt researchers sought to examine cardiovascular deaths in patients who were taking the antibiotic.

Tennessee Medicaid (TennCare) patient records were examined from 1992 to 2006.

The researchers took many steps in this large, observational, population-based study to rule out other reasons for the increase in cardiovascular deaths in patients taking azithromycin. About 348,000 recorded prescriptions of azithromycin were compared with millions of similar records from people who were not treated with antibiotics or were treated with other antibiotics. The primary comparison was with amoxicillin, an antibiotic that is considered to be heart safe and is used in similar clinical circumstances as azithromycin.

While the absolute number of deaths was quite low, relative to amoxicillin, there were about 47 more deaths per million courses of therapy in those taking the azithromycin. That risk increased to 245 additional cardiovascular deaths per million in patients already known to have a high risk for heart problems.

The researchers emphasized that the decision to prescribe any antibiotic requires careful balancing of both potential benefits and risks. This calculation must consider the severity of the infection, the susceptibility of the organism, the availability of alternative antibiotics and adverse effects.

"We believe this study adds important information on the risk profile for azithromycin," said Ray. "For patients with elevated cardiovascular risk and infections for which there are alternative antibiotics, the cardiovascular effects of azithromycin may be an important clinical consideration."

Hormone-depleting drug shows promise against localized high-risk prostate tumors

BOSTON—A hormone-depleting drug approved last year for the treatment of metastatic prostate cancer can help eliminate or nearly eliminate tumors in many patients with aggressive cancers that have yet to spread beyond the prostate, according to a clinical study to be presented at the annual meeting of the American Society of Clinical Oncology (ASCO), June 1-5, in Chicago.

The phase II clinical trial, led by investigators at Dana-Farber Cancer Institute and other research centers, examined the use of the drug abiraterone acetate (Zytiga(R)) in combination with prednisone and surgery in 58 men with high-risk prostate cancer isolated to the prostate gland. Participants received either three or six months of the two-drug regimen followed by surgery to remove the prostate. When the treatment was complete, pathology exams showed that one-third of the participants had no or almost no tumor tissue left.

"Very high-risk cancers localized to the prostate are rarely cured by prostatectomy alone," says the study's lead author, Mary-Ellen Taplin, MD, of Dana-Farber. "Therapies that combine surgery with older androgen-inhibiting drugs have not historically improved outcomes. This unmet need has given rise to efforts to develop new drugs capable of more completely reducing androgen levels within the prostate tumors."

Taplin will present the data (abstract 4521) on Saturday, June 2, at 8 a.m. CT, Arie Crown Theater, McCormick Place.

Androgen, the male hormone, provides the fuel for prostate cancer growth. Conventional therapies target androgen production in the testes and adrenal glands, but not within the tumor itself. Abiraterone acetate is capable of blocking androgen production in all three sites.

In the study, researchers used half the dose of prednisone (a steroid) standardly given with abiraterone acetate. This lower dose, it is hoped, would reduce the side effects associated with steroids while maintaining its benefits of protecting particular steroid imbalances associated with abiraterone. Since there were no increased side effects from abiraterone, the researchers feel that the lower dose of prednisone (5mg daily) is adequate for most patients.

"Most of the patients in this study had large tumors, high grade prostate cancers and were at high risk for cancer spread," Taplin remarks. "We're very encouraged by the results and have begun another phase II study investigating another novel androgen signaling inhibitor, MDV3100, in the neoadjuvant setting for high risk prostate cancer. We are also developing a clinical trial program investigating the addition of
the investigational drug ARN509 to abiraterone. To prove the overall benefit of intensive androgen deprivation treatment in conjunction with prostatectomy, a large randomized clinical trial will need to be done."

**DNA Replication Protein Also Has a Role in Mitosis, Cancer**

ScienceDaily (May 13, 2012) — The foundation of biological inheritance is DNA replication—a tightly coordinated process in which DNA is simultaneously copied at hundreds of thousands of different sites across the genome. If that copying mechanism doesn’t work as it should, the result could be cells with missing or extra genetic material, a hallmark of the genomic instability seen in most birth defects and cancers.

University of North Carolina School of Medicine scientists have discovered that a protein known as Cdt1, which is required for DNA replication, also plays an important role in a later step of the cell cycle, mitosis. The finding presents a possible explanation for why so many cancers possess not just genomic instability, but also more or less than the usual 46 DNA-containing chromosomes.

The new research, which was published online ahead of print by the journal *Nature Cell Biology*, is the first to definitively show such a dual role for a DNA replication protein.

"It was such a surprise, because we thought we knew what this protein’s job was—to load proteins onto the DNA in preparation for replication,” said Jean Cook, PhD, associate professor of biochemistry and biophysics and pharmacology at the UNC School of Medicine and senior study author. "We had no idea it also had a night job, in a completely separate part of the cell cycle.”

The cell cycle is the series of events that take place in a cell leading to its growth, replication and division into two daughter cells. It consists of four distinct phases: G1 (Gap 1), S (DNA synthesis), M (mitosis) and G2 (Gap 2). Cook’s research focuses on G1, when Cdt1 places proteins onto the genetic material to get it ready to be copied.

In this study, Cook ran a molecular screen to identify other proteins that Cdt1 might be interacting with inside the cell. She expected to just find more entities that controlled replication, and was surprised to discover one that was involved in mitosis. That protein, called Hec1 for "highly expressed in cancer," helps to ensure that the duplicated chromosomes are equally divided into daughter cells during mitosis, or cell division. Cook hypothesized that either Hec1 had a job in DNA replication that nobody knew about, or that Cdt1 was the one with the side business.

Cook partnered with Hec1 expert Edward (Ted) D. Salmon, PhD, professor of biology and co-senior author in this study, to explore these two possibilities. After letting Cdt1 do its replication job, the researchers interfered with the protein’s function to see if it adversely affected mitosis. Using a high-powered microscope that records images of live cells, they showed that cells where Cdt1 function had been blocked did not undergo mitosis properly.

Once the researchers knew that Cdt1 was involved in mitosis, they wanted to pinpoint its role in that critical process. They further combined their genetic, microscopy and computational methods to demonstrate that without Cdt1, Hec1 fails to adopt the conformation inside the cells necessary to connect the chromosomes with the structure that pulls them apart into their separate daughter cells.

Cook says cells that make aberrant amounts of Cdt1, like that seen in cancer, can therefore experience problems in both replication and mitosis. One current clinical trial is actually trying to ramp up the amount of Cdt1 in cancer cells, in the hopes of pushing them from an already precarious position into a fatal one.

**Journal Reference:**
the loop domain of Hec1 is required for stable kinetochore–microtubule attachment. Nature Cell Biology, 2012; DOI:
10.1038/ncb2489

**Novel RNA Transport Mechanism: Ribonucleoprotein Granules Exit the Nucleus Via a Budding Mechanism**

ScienceDaily (May 10, 2012) — The movement of genetic materials, such as RNA and ribosomes, from the nucleus to the cytoplasm is a critical component in a cell's ability to make the proteins necessary for essential biological functions. Until now, it was believed the nuclear pore complex was the sole pathway between the cell nucleus and cytoplasm for these materials.

New evidence published in *Cell* by Vivian Budnik, PhD, professor of neurobiology, Melissa J. Moore, PhD, the Eleanor Eustis Farrington Chair in Cancer Research, Howard Hughes Medical Institute Investigator and professor of biochemistry & molecular pharmacology, and colleagues, reveals a novel budding mechanism, similar to the process used by some viruses, capable of exporting large ribonucleoprotein (RNP) particles from the nucleus to the cytoplasm.

"The findings in this paper fundamentally change our understanding of mRNA export from the nucleus," said Dr. Moore. "In addition to the canonical pathway of mRNA export going through the nuclear pore complex, we now know that large RNA transport granules can be assembled in the cell nucleus and exported via a budding mechanism previously thought to only be used by the herpes virus."

This study has helped to unravel how RNAs support the development of the post-synaptic apparatus, said Dr. Budnik. "It provides new evidence about communication between the nucleus and cytoplasm that has implications for diseases that affect the nuclear envelope such as muscular dystrophies and herpes-type infections such as shingles."

Found along the surface of the nuclear envelope, nuclear pores are small openings that allow certain molecules, such as messenger RNA, transfer RNA and ribosomes, to be transported across this physical barrier that separates a cell’s nucleus and DNA from its cytoplasm. Once in the cytoplasm, these genetic materials are the factories and blueprints used by the cell to create proteins. In some cells, these RNAs are bound together in large clusters known as transport granules, which are carried to precise locations within a cell to synthesize specific proteins needed at that site.

"When we look at these transport granules to scale, we see that they're too large to pass through the nuclear pore complex," said Moore. "An open question has been, where are these transport granules first assembled? And if it's in the nucleus, how do they make their way to the cytoplasm?"

Working to understand how synapses develop and communicate with neighboring muscle cells, Budnik discovered a new method whereby these large granules, in the form of RNP particles, were transported across the nuclear envelope. Specifically, Budnik and colleagues were investigating how the Wnt/wingless (Wg) protein secreted by the motor neuron initiates a reaction involving the DFrizzled2 (DFz2) receptor on the nearby muscle cell. This interaction between Wg and DFz2 eventually leads a portion of the DFz2 into the muscle cell nucleus where it accumulates around large RNP granules containing messenger RNAs. Once they reach their final destination in the muscle cell cytoplasm, these RNAs are responsible for making the synaptic proteins critical to increasing the size of the junction between motor neuron and muscle cell.

It was while investigating this process that Budnik and colleagues witnessed these large granules exiting the muscle cell's nucleus in an unusual manner. "What was so surprising," said Sean D. Speese, PhD, former postdoctoral fellow in the Budnik lab and currently research assistant professor at Oregon Health and Sciences University, "was that the nuclear DFz2-large–RNP's utilized a novel mechanism for exiting the nucleus, which appeared independent of the nuclear pores and resembled the egress of herpes-type viruses from the nuclear envelope."

During infection, herpes virus particles are assembled in the nucleus. But they are much too large to exit through the nuclear pores. Instead, they bud through the double membranes of the nuclear envelope. To exit the nucleus, the protein shell surrounding the virus disrupts the lamina, a fibrous component located beneath the inner nuclear membrane which, among other properties, anchors the nuclear pore complexes to the nuclear membranes. This allows the virus to bud into the space between the inner and the outer nuclear membrane, becoming enveloped by the inner nuclear membrane. Fusion of this coat with the outer nuclear membrane then allows the virus to be released into the cytoplasm.

"Similarly, we found that DFz2C-RNPs used the same mechanism and viral machinery to reach the cytoplasm," said Dr. Speese. Once inside the muscle cell nucleus, the DFz2C RNPs recruit proteins, such as kinase C, to disrupt the lamins, which allows them to bud into the inner nuclear membrane. "In both
cases, this process was dependent on an A-type lamina protein, which in humans is associated with a number of muscular dystrophies and early aging syndromes when mutated,” said Speese.

Collectively, these discoveries have significant ramifications for our understanding of multiple biological questions including RNA transport, synapse development and the herpes virus, which causes chicken pox and shingles as well as Epstein-Barr virus, which causes mononucleosis.

**Journal Reference:**
Sean D. Speese, James Ashley, Vahbiz Jokhi, John Nunnari, Romina Barria, Yihang Li, Bulent Ataman, Alex Koon, Young-Tae Chang, Qian Li, Melissa J. Moore, Vivian Budnik. **Nuclear Envelope Budding Enables Large Ribonucleoprotein Particle Export during Synaptic Wnt Signaling.** *Cell*, 2012; 149 (4): 832 DOI: [10.1016/j.cell.2012.04.032](https://doi.org/10.1016/j.cell.2012.04.032)

**PLoS Pathogens**

**Age of the Association between *Helicobacter pylori* and Man**

**Abstract**

When modern humans left Africa ca. 60,000 years ago (60 kya), they were already infected with *Helicobacter pylori*, and these bacteria have subsequently diversified in parallel with their human hosts. But how long were humans infected by *H. pylori* prior to the out-of-Africa event? Did this co-evolution predate the emergence of modern humans, spanning the species divide? To answer these questions, we investigated the diversity of *H. pylori* in Africa, where both humans and *H. pylori* originated. Three distinct *H. pylori* populations are native to Africa: hpNEAfrica in Afro-Asiatic and Nilo-Saharan speakers, hpAfrica1 in Niger-Congo speakers and hpAfrica2 in South Africa. Rather than representing a sustained co-evolution over millions of years, we find that the coalescent for all *H. pylori* plus its closest relative *H. acinonychis* dates to 88–116 kya. At that time the phylogeny split into two primary super-lineages, one of which is associated with the former hunter-gatherers in southern Africa known as the San. *H. acinonychis*, which infects large felines, resulted from a later host jump from the San, 43–56 kya. These dating estimates, together with striking phylogenetic and quantitative human-bacterial similarities show that *H. pylori* is approximately as old as are anatomically modern humans. They also suggest that *H. pylori* may have been acquired via a single host jump from an unknown, non-human host. We also find evidence for a second Out of Africa migration in the last 52,000 years, because hpEurope is a hybrid population between hpAsiatic and hpNEAfrica, the latter of which arose in northeast Africa 36–52 kya, after the Out of Africa migrations around 60 kya.

**Author Summary**

We previously showed that the population history of *H. pylori* may be used as a marker for human migrations, including the demonstration that humans carried *H. pylori* out of Africa 60,000 years ago during their recent global expansions. But how long were humans infected by *H. pylori* prior to the out-of-Africa event? Here we showed that chimpanzees in Central-East Africa do not possess *Helicobacter*-like bacteria, as would have been expected for pathogen-host co-evolution over millions of years. Using *H. pylori* gene sequences isolated from San, a group of click-speaking hunter-gatherers, and numerous other sources, we calculated that humans have been infected with *H. pylori* for at least 88,000–116,000 years. Phylogenetic comparisons showed similar evolutionary histories for human and *H. pylori* lineages and suggest that this association stemmed from a single host jump. We showed that hpAfrica2, the most divergent *H. pylori* population, arose in the San and that their progenitors were the source of *H. acinonychis* which was acquired by large felines approximately 50,000 years ago. Furthermore, our data provided clear evidence for a recent second exodus Out of Africa in the last 52,000 years which was essential for the formation of the hybrid population that currently infects Europeans.

**Broad-Spectrum Antivirals: The Future of HIV Treatment?**

By Warren Tong

May 16, 2012

Could a single drug be used to treat a variety of viruses—potentially all viruses, including HIV? At least three novel approaches are being worked on to create such a drug, also known as a broad-spectrum antiviral.

Broad-spectrum drugs already exist in other areas of medicine. For instance, we have antibiotics to treat a wide range of bacterial infections. Unfortunately, while antibiotics work great at thwarting bacteria, they are largely ineffective against viruses.

Presently we have different antivirals that tend to treat specific diseases (e.g., Tamiflu only treats influenza, and most HIV medications only treat HIV). However, as people with HIV are well aware, viruses mutate and grow resistant to current antivirals.
WIRED recently published an article highlighting three new approaches to antiviral treatment that may be able to stop a wide range of viruses, but without the risk of the viruses becoming resistant.

Prosetta: Chipping Away the Virus’s Shell
Before he founded the biotech company Prosetta, researcher Vishwanath Lingappa, M.D., Ph.D., realized that viruses use proteins, taken from the very host cells they infected, as building blocks in producing the protective shells that exist around new, replicated viruses. Lingappa used this knowledge as a basis for his attempt to develop a broad-spectrum antiviral.

Instead of developing a drug to target the virus itself, which could then evolve and grow resistant, Prosetta's approach aims to alter the proteins in our own cells—without damaging our cells in the process. "Prosetta’s molecules bind to the proteins that viruses need to create their shells, stopping the maturation process. And because these proteins come together only to make viruses, the drugs should be nontoxic to patients," WIRED reports.

When asked how Prosetta’s drug might fare against HIV, Lingappa told TheBody.com, "Our approach appears to work for all families of viruses, including the Retroviridae, of which HIV is a member. One of the nice things about this approach is that resistance is extremely unlikely to develop to these compounds, since they target the host, not the virus. Moreover, the compounds appear to do so in ways that are essential for the virus but not for the host."

Lingappa added that his team has been able to identify chemical compounds "that have proven highly active against HIV" in lab tests, and he is excited for Prosetta’s potential in terms of a possible cure for HIV. But he also knows there is a long road ahead.

Interferon: The Next Generation
People living with hepatitis C are likely familiar with interferon, which has been a fundamental part of hep C treatment for years. Interferon is a protein made by our immune system to fight off viruses, bacteria, tumors and other unwelcome visitors. Interferon treatments, such as PegIntron and Pegasys, boost the body's ability to fight back.

However, many viruses prevent interferons from being made. And interferon treatments on the market often have their limitations and side effects.

Eleanor Fish, Ph.D. of the University of Toronto and other researchers are looking into developing a better version. "They've created synthetic interferons that last days instead of hours and will wipe out hepatitis C viruses completely in up to 81 percent of treated patients, depending on the strain," WIRED reports. "During Toronto’s SARS outbreak, Fish tested synthetic interferons on a small pool of patients and found that their lungs healed significantly faster than those of control patients."

These preliminary results are promising and more research could lead to a very effective broad-spectrum antiviral. (TheBody.com attempted to reach Fish to discuss how her approach might apply specifically to HIV, but was unable to do so before this article was posted.)

DRACO: The Kamikaze-Cell Approach
The third and perhaps most interesting method reported in WIRED is an antiviral in development named DRACO (Double-stranded RNA (dsRNA) Activated Caspase Oligomerizer). It is being engineered to do two things: identify cells that are infected with a virus and trigger those infected cells to commit suicide. "Because viruses have never been exposed to Draco before, their counterattacks are useless. The infected cells die before the viruses can mature," WIRED notes.

In a paper published in PLoS One last July, lead researcher Todd Rider, Ph.D., and his team at the Massachusetts Institute of Technology (MIT) explained the science behind DRACO: The drug "selectively induces apoptosis in cells containing viral dsRNA, rapidly killing infected cells without harming uninfected cells," they write. Lab testing has "shown that the DRACOs are nontoxic in 11 mammalian cell types and effective against 15 different viruses, including dengue flavivirus, Amapari and Tacaribe arenaviruses, Guama bunyavirus, and H1N1 influenza."

DRACO has not been tested against HIV yet, but Rider told TheBody.com, "We have recently established collaborations to test DRACO against HIV and several other viruses of interest. We certainly hope that DRACO will be effective against HIV, and that it can be a true cure for the virus."

However, while Rider is hopeful, he added that his drug is still a very long way from being proven effective in humans. "Even in the best case, MIT, our collaborators, and companies to which we license this technology will need to do several more years of animal trials before any human drug trials can begin,
and then the human trials will probably take at least a few years before DRACO could be approved for everyone to use."

So, while all three of these approaches show a lot of promise, we shouldn't get our hopes up just yet. There are dangers to be wary of. For instance, we still don't fully understand the viral ecology in our bodies. Just like some bacteria naturally live inside our bodies and are helpful to our health, we may also be a home for "good" viruses that we don't know about, but that help us stay healthy and maintain our bodies' equilibrium. Still, further research on these approaches is definitely welcome. Hopefully more good results will follow.

**New Technique Reveals Unseen Information in DNA Code**

ScienceDaily (May 17, 2012) — Imagine reading an entire book, but then realizing that your glasses did not allow you to distinguish "g" from "q." What details did you miss?

Geneticists faced a similar problem with the recent discovery of a "sixth nucleotide" in the DNA alphabet. Two modifications of cytosine, one of the four bases that make up DNA, look almost the same but mean different things. But scientists lacked a way of reading DNA, letter by letter, and detecting precisely where these modifications are found in particular tissues or cell types.

Now, a team of scientists from the University of Chicago, the Ludwig Institute for Cancer Research, the University of California, San Diego and Emory University has developed and tested a technique to accomplish this task. The results are published May 17 in the online edition of the journal *Cell*.

The team used the technique to map 5-methylcytosine (5-mC) and 5-hydroxymethylcytosine (5-hmC) in DNA from human and mouse embryonic stem cells, revealing new information about their patterns of distribution. These studies have revealed that these DNA modifications play major roles in fundamental life processes such as cell differentiation, cancer and brain function.

"They regulate gene expression and have a broad impact on stem cell development, various human diseases such as cancer, and potentially on neurodegenerative disease. They may even shape the development of the human brain," said Chuan He, professor in chemistry at UChicago.

Scientists have been examining the patterns of 5-mC for decades, as part of the field of epigenetics: the study of the information that lies "on top" of the DNA sequence. However, researchers only recognized that 5-hmC was present at significant levels in our DNA a few years ago. 5-mC is generally found on genes that are turned off, and helps silence genes that aren't supposed to be turned on. In contrast, 5-hmC appears to be enriched on active genes, especially in brain cells. Also, defects in the Tet enzymes that convert 5-mC into 5-hmC can drive leukemia formation, hinting that changes in 5-hmC are important in cancer.

The *Cell* paper describes a method called TAB-Seq that directly measures 5-hmC, and presents the first map of the entire genome of 5-hmC at single-base resolution. DNA modifications in 5-hmC play key roles in processes fundamental to life. (Credit: Chuan He)
The other two laboratories of the team, Bing Ren’s Ludwig Institute for Cancer Research/UCSD group applied TAB-Seq to human embryonic stem cells, while Peng Jin’s group at Emory University applied the method to mouse embryonic stem cells.

Previous studies had shown that 5-hmC was found on genes that are turned on. Now, the additional resolution and subsequent research on mouse and human embryonic stem cells reveals that it is found most often on the stretches of DNA that control a gene’s activity, called enhancers, in comparison with the parts of genes that are actually read out into RNA.

“We learned using this new technique that this modification is most abundant in the areas of the genome known as enhancers, which regulate the expression of genes. This potential regulatory role of hmC may explain its importance in embryonic stem cells, and why its disruption may result in the development of leukemia,” said Gary Hon, a postdoctoral fellow in the laboratory of Bing Ren, who carried out the genome-wide analysis of 5hmC in the human embryonic stem cells at the Ludwig Institute for Cancer Research at UCSD.

Another difference with 5-mC is that 5-hmC is usually on only one side of the DNA. In contrast, 5-mC is most often found symmetrically. Overall, 5-hmC is around 14 times less abundant than 5-mC. Even at sites where 5-hmC is the most abundant, it is still present at about one fifth the frequency as 5-mC, the team found using the new technique.

Previous research has found that 5-hmC is 10 times more abundant in brain than in stem cells, so it may have an especially important role there. Jin’s laboratory is using the new technique to finely map 5-hmC in the developing brain.

“To really see the kinds of functions 5-hmC can have, we need to look at how it appears and disappears over time, during processes like brain development. This technique will allow us, and other investigators, to dive in and get that information at high resolution," said Jin, an associate professor of human genetics at Emory.

Journal Reference:
Miao Yu, Gary C. Hon, Keith E. Szulwach, Chun-Xiao Song, Liang Zhang, Audrey Kim, Xuekun Li, Qing Dai, Yin Shen, Beomseok Park, Jung-Hyun Min, Peng Jin, Bing Ren, Chuan He. **Base-Resolution Analysis of 5-Hydroxymethylcytosine in the Mammalian Genome.** *Cell,* 2012; DOI: 10.1016/j.cell.2012.04.027

Experts call for clinical trials to test non-skeletal benefits of vitamin D
Observational studies show vitamin D may benefit cardiovascular, skin and metabolic disorders
Chevy Chase, MD—The Endocrine Society’s new scientific statement published online today represents the first comprehensive evaluation of both the basic and clinical evidence related to the non-skeletal effects of vitamin D. The statement addresses current research regarding the associations of vitamin D with immune function, hypertension, stroke, skin conditions and maternal/fetal health.

Vitamin D is a steroid hormone that regulates calcium and phosphate levels in the bloodstream and promotes healthy bone growth. Vitamin D deficiency is common throughout the world and results in abnormalities of calcium, phosphorus and bone metabolism which can lead to muscle weakness, osteomalacia, osteopenia and osteoporosis. While some observational studies have shown that benefits of vitamin D may extend beyond bone health, research findings remain inconsistent.

"The role of vitamin D supplementation in the prevention and treatment of chronic non-skeletal diseases remains to be determined," says Clifford Rosen, MD, of Tufts University School of Medicine and chair of the task force that authored the statement. "We need large randomized controlled trials and dose-response data to test the effects of vitamin D on chronic disease outcomes including autoimmunity, obesity, diabetes, hypertension and heart disease."

The scientific statement outlines the evidence that defines the effects of vitamin D on epidermal, neuromuscular, maternal/fetal and neoplastic (abnormal growth) tissues. The authors critically evaluated the literature for each organ system utilizing available evidence from observational studies and randomized trials to determine the strength of associations between vitamin D and tissue-specific outcomes.

Conclusions from the statement include:
- Topical and oral vitamin D may be useful in treating skin disorders such as psoriasis, though large-scale randomized placebo-controlled clinical trials are needed to demonstrate the efficacy of treatment with vitamin D on skin disorders or the prevention of skin cancer.
- The ever-expanding obesity epidemic has been associated with a rising prevalence of vitamin D deficiency, but a cause-and-effect relationship has not been established. Strong evidence does not
exist to support the tenet that vitamin D supplementation reduces the risk of type 2 diabetes or the metabolic syndrome.

- Vitamin D supplementation is likely to reduce the risk of falls, particularly in individuals who have low baseline levels (<20 ng/ml) and are supplemented with calcium as well.
- Recent systematic reviews have found that evidence that vitamin D reduces cancer incidence are inconclusive as to causality. Observational evidence is strongest for colorectal cancer but is weak or inconsistent for breast, prostate and total cancer.
- There is a possibility that vitamin D supplementation may lower cardiovascular disease risk, but there are limitations in applying observational data to clinical practice. An insufficiency of evidence from clinical trials does not support recommending vitamin D supplementation for lowering cardiovascular disease risk at this time.
- Clinical trials are needed to test whether vitamin D supplementation during pregnancy will prevent type 1 diabetes in offspring.


Health Experts Narrow the Hunt for Ebola
ScienceDaily (May 16, 2012) — Response efforts to outbreaks of Ebola hemorrhagic fever in Africa can benefit from a standardized sampling strategy that focuses on the carcasses of gorillas, chimpanzees, and other species known to succumb to the virus, according to a consortium of wildlife health experts.

In a recently published study of 14 previous human Ebola outbreaks and the responses of wildlife teams collecting animal samples, the authors of the new study conclude that most efforts to collect samples from live animals (i.e. rodents, bats, primates, birds) failed to isolate Ebola virus or antibodies. However, they found that collecting samples from animal carcasses during outbreaks was a more effective method for Ebola detection. The early detection of Ebola in animal populations near a human outbreak is crucial for learning more about this virus, which can strike human populations with a mortality rate of more than 80 percent.

"You can't test every single animal, so we used information from historical outbreaks to figure out how to help the field response team focus their effort," according to Wildlife Conservation Society (WCS) wildlife epidemiologist Sarah Olson, the lead author of the new report. "It turns out that carcass sampling yields a 50 percent chance of finding Ebola virus or antibodies compared to less than six percent when sampling free-ranging live animals."

The scientific consortium that participated in the study, published in an online issue of Emerging Health Threats, are key partners in PREDICT, part of USAID's Emerging Pandemic Threats Program that is improving global capacity to respond to emerging infectious diseases that originate in wildlife. PREDICT is led by the University of California at Davis, in partnership with Ecohealth Alliance, Global Viral Forecasting Initiative, the Smithsonian Institution, and the Wildlife Conservation Society.

"The Emerging Pandemic Threats program is a visionary investment by USAID to protect and improve global health because it has made it possible for us to, for the first time, preemptively, and on a global scale, identify novel pathogens in wildlife that could pose pandemic threats to humans," said Dr. Jonna Mazet, Director of PREDICT and Director of the One Health Institute at the University of California, Davis School of Veterinary medicine. "This study is a great example of how PREDICT is using science to improve our ability to detect lethal diseases, like Ebola."

The study was designed to develop a set of animal sampling recommendations to maximize the effectiveness of Ebola outbreak response efforts with limited resources. Specifically, the study was prompted by a 2011 outbreak near Kampala, Uganda, in which a 12-year-old girl died from Ebola hemorrhagic fever. PREDICT wildlife veterinarians were sent to the victim's village to screen wildlife as a potential source of the virus.

"This study digests over 30 years of accumulated knowledge so field teams can arrive informed and prepared," adds WCS epidemiologist and senior author, Damien Joly.

The authors also point to some scientific "loose ends" that can be incorporated into future animal sampling efforts during Ebola outbreak response. For instance, despite some evidence of Ebola in dogs and pigs, the number of samples acquired from these animals is limited to just two outbreaks; the authors recommend increasing the number of samples collected from these groups in the future to better determine their role in Ebola outbreaks. The study also confirms that while fruit bats should be a focus of investigation as a potential reservoir for Ebola, field teams need...
to be prepared to sample hundreds of bats because virus prevalence across all bats sampled to date is very low, estimated at 3 percent.

Journal Reference:
Sarah H. Olson, Patricia Reed, Kenneth N. Cameron, Benard J. Ssebide, Christine K. Johnson, Stephen S. Morse, William B. Karesh, Jonna A. K. Mazet, Damien O. Joly. Dead or alive: animal sampling during Ebola hemorrhagic fever outbreaks in humans. Emerging Health Threats Journal, 2012; 5 (0) DOI: 10.3402/ehtj.v5i0.9134

Six Threats to Chromosomes
Researchers identify two new DNA repair systems, in addition to four that were already known, that can attack unprotected telomeres.
By Ed Yong | May 3, 2012

For decades, scientists have known that chromosomes are protected by repetitive DNA known as telomeres, which themselves are protected by a cap of six proteins called shelterin. Now, researchers in New York have shown what shelterin protects chromosomes from—six different DNA repair systems, including two not previously known to attack telomeres.

The study, published today (May 3) in Science, “represents the closing of one chapter in understanding telomere biology,” said biochemist Steve Jackson from the University of Cambridge, who was not involved in the work. Though the results weren’t unexpected, added biochemist Stéphane Marcand from the University of Oxford, “the data in this paper provide a synthesis of the past 10 to 15 years of research in the field.”

Telomeric sequences at the ends of chromosomes protect the coding DNA from erosion during DNA replication. Telomeres are believed to dictate a cell’s lifespan, and have been linked to a handful of diseases. (See this month’s feature, “Telomeres in Disease.”) But the role of the shelterin cap in protecting telomeres has been somewhat unclear.

Previous research identified four repair pathways that mistake telomeres for damaged DNA, and enact molecular protocols designed to repair that damage. These wrongly attempted fixes can lead to genetic abnormalities that could increase the risk of cancer. Two of these—homologous recombination (HR) and non-homologous end-joining (NHEJ)—are different routes for fixing the supposed damage. The other two involve the ATM and ATR genes, which initiate a chain of events that stops cells from growing and dividing.

But these experiments all involved removing each of the shelterin proteins one at a time, which led Agnel Sfeir, currently at New York University School of Medicine, to suspect that scientists were missing something—what if the remaining shelterin proteins were compensating for the loss of any single member? Working with Titia de Lange from the Rockefeller University and managed to remove the entire group by getting rid of the two members that anchor the rest to the telomere, TRF1 and TRF2. The researchers also had to knock out other proteins that would fuse the uncapped telomeres together, to allow them to figure out what happens to the naked ends.

Sfeir was adamant on this approach, even though it took her several years to breed the right mice. “It’s an awful experiment to do,” said de Lange, amazed Sfeir insisted on taking it on. “I wouldn’t have subjected anyone else in my lab to it.”

The experiment revealed that uncapped ends are vulnerable to six—not four—different repair systems. One of the previously overlooked pathways is an alternative way of joining two ends, known as alt-NHEJ. The other involves cutting back one of the exposed DNA strands, a process known as hyperresection.
“Our work describes the full spectrum of events that could happen at chromosome ends that have lost telomere protection,” said de Lange. “There aren’t four pathways, but six, that pose a threat to the integrity of the chromosome end, and that telomeres must protect against.”

Shortened or damaged telomeres are a hallmark of the cellular aging process, as well as many diseases including cancers and dyskeratosis congenita, an inherited disorder that causes premature aging. The researchers hope that by revealing the pathways that threaten unprotected DNA ends, they can better understand the early stages of these conditions, and find new avenues to treat them.

There are still a lot to learn about shelterin. For instance, how the structure of its components contribute to their function, how the complex is controlled under different circumstances, and how it misbehaves to cause disease are still open questions. “There remains much else to be understood,” says Jackson.


What Bugs Are in Your Gut?
Hundreds of samples of human feces reveal how gut microbes change as we age and vary between people in different countries.
By Ruth Williams | May 9, 2012
Humans from different cultures and geographic locations differ in the diversity of bacteria in their guts, but the metabolic functions that those microbial communities serve are similar, according to a report out in Nature today (May 9). The findings come from a large-scale sequencing project carried out on 531 samples of human excrement from Africa, South America, and the United States.

“It’s a humungous paper, with multiple key findings,” said food scientist David Mills of the University of California, Davis. “An impressive and complex piece of work,” agreed molecular biologist Jeremy Nicholson of Imperial College, London. Neither researcher participated in the study.

The scale and complexity stem from the research team’s aim of answering a multifaceted question—“What is the degree to which these microbial communities... vary within a person, as a function of postnatal development, physiological status, cultural tradition, and where a person lives,” said geneticist Jeffrey Gordon of the Washington University in St Louis, who led the study.

To this end, the researchers collected samples of feces from villagers in rural Malawi, Amerindians in Amazonian Venezuela, and metropolis-dwelling Americans. They then performed high-throughput sequencing on DNA taken from the samples to determine both the species and strains of microbes present and which microbial genes were most abundant.

The team found a common pattern for how the microbiomes of babies develop in three countries. “It takes 6 to 9 months to get the first 6 or 700 bugs and then another couple of years to get the adult set,” explained Nicholson. “[Gordon] finds there is the same sort of developmental time span between countries,” he said, “but that the resulting microbiomes are nonetheless distinct between, let’s call it, a third-world population and a westernized population.”

One of the most striking differences was the degree of microbial diversity, with both the Amerindians and Malawians having far greater diversity than the Americans. “But, ironically, [Americans] might have more diversity in terms of the food eaten,” said Mills, which might have been expected to correlate with microbial diversity. Gordon suggested the Westerners’ lack of diversity could result from “our lifestyle, our degree of hygiene, [and] our use of antibiotics,” though further research is needed to test these possibilities.

Despite these differences between the gut microbiomes of the three cultures, there were also striking similarities, said Gordon. For example, “across all three populations, we see this age-dependent change in vitamin biosynthesis,” he said. In infants, gut bacteria tend to carry more copies of genes involved in folate biosynthesis, while the guts of older individuals harbor microbes carrying more genes for folate metabolism. Conversely, genes involved in vitamin B-12 synthesis became more prevalent in the gut microbiome with age.

“What’s really fascinating about those results,” said Mills, “is that it is reflecting what the host needs.”

The documenting and detailing of human microbiomes across ages and cultures is an important resource for future studies, Mills added. One obvious question arising from the work is, what difference do these bugs make, if any, to people’s health? According to a presentation by Liene Bervoets at the the 19th European Congress on Obesity in Lyon, France, this week, obese children have a markedly different proportions of the bacteria Bacteroidesfragilis and Bacteroidesvulgatus in their guts than normal weight children. “Whether changes in gut microbiota are a cause or consequence
of obesity remains to be established, but it is clear that the microbiota aid in energy harvesting from our foods,” Bervoets said in an email to The Scientist.

Gordon and his team now plan to investigate how variations in our gut microbiomes might affect such energy harvesting. “Our long term hope... is to understand the inter-relationship between the microbiome, the nutritional value of foods that are consumed, and the nutritional status of people,” he said.


Comment:
Richard Spencer Collapse
What would be a useful application of these findings would be to design proactive microbiome supplements akin to acidophilus milk that could protect short-term and long-term travelers against food- and water-borne unwanted microbiomes that cause potentially dangerous gastrointestinal distress and dehydration.

agelbert, Retired Air Traffic Controller
Scientists need to relearn the value to the environment of gut bacteria and the feces they populate and help create. The fact is that our so called "waste" is a step in the ecological cycle that is vital for our survival. Calling it "waste" is unscientific because it takes an anthropomorphic view in an ecosphere that science has proven thrives ONLY through the interconnection of species nutrients. A more properly descriptive term is "humanure".

http://www.lowtechmagazine.com...

Snippet 1:
[For 4,000 years, human excrements and urine were considered extremely valuable trade products in China, Korea and Japan. Human dung was transported over specially designed canal networks by boats. Thanks to the application of human "waste" products as fertilizers to agricultural fields, the East managed to feed a large population without polluting their drinking water. Meanwhile, cities in medieval Europe turned into open sewers. The concept was modernized in late 19th century Holland, with Charles Liernur's sophisticated vacuum sewer system.]

Snippet 2:
[Human faeces and urine can only be used as a fertilizer following further treatment. This was an already known fact by early Chinese agricultural writers, who warned that untreated humanure could "burn and kill plants, rot the shoots and harm human hands and feet". Today we know it also carries more severe health risks. F.H. King and Joseph Needham praise the composting efforts of the early Chinese, who often combined their privy with the family pigsty (see illustration below). However, Duncan Brown is more critical of their composting techniques. The health advantages that the Chinese gained by keeping their drinking water supplies clean, were partly offset by the transmission of diseases via food crops:

"Gastro-intestinal diseases were endemic throughout the region. In Korea and Japan, fluke diseases were common because of the practice of eating raw fish grown in ponds fertilized with human excrement. But those diseases could have been largely avoided with a better understanding of their nature and modes of transmission. If properly used, devices like the relatively modern septic tank, the more modern oxidation tank or the so-called composting toilet can avoid the danger of gastro-intestinal diseases previously associated with the use of human excrement as manure."

Snippet 3:
[Can we feed the world using humanure?
Can we produce enough natural fertilizer to substitute for synthetic nitrogen and mined potassium and phosphates? According to the figures collected by F.H. King, an adult person produces on average 1,135 grams of dung and urine each day. How much nitrogen, potassium and phosphates does this contain? That all depends on the diet.]

Snippet 4:
[Nutrient balance
Let's digest all this information for a second. On the one hand, we have livestock and people, who together produce 166 million tonnes of nitrogen and 72 million tonnes of phosphates. Almost all of this is wasted, wreaking ecological havoc.

At the same time, our factories produce 99.9 million tonnes of artificial nitrogen fertilizer and 37 million tonnes of phosphates.

A completely superfluous operation that further increases pollution and consumes vast amounts of energy. With the expected human (and livestock) population growth, not to mention the rise of energy crops to make biofuels, both biological and artificial production will rise even further, making everything only worse.

Full article here: http://www.lowtechmagazine.com...

John Michael Keating Collapse
Interesting, but it should have included any changes related to antibiotic use. I wonder if my fairly recent obesity is due to antibiotics having eliminated my (healthy) microbiota allowing the installation of a set that "improves" food usage by my body. So, if yes, food supplements to reinstall previous "companions" would be useful.

Synthetic Genetic Evolution
Scientists show that manmade nucleic acids can replicate and evolve, ushering in a new era in synthetic biology.

By Ruth Williams | April 19, 2012
Synthetic genetic polymers, broadly referred to as XNAs, can replicate and evolve just like their naturally occurring counterparts, DNA and RNA, according to a new study published today (April 19) in Science. The results of the research have implications not only for the fields of biotechnology and drug design, but also for research into the origins of life—on this planet and beyond.

“It’s a breakthrough,” said Gerald Joyce of The Scripps Research Institute in La Jolla, California, who was not involved in the study—“a beautiful paper in the realm of synthetic biology.”
“It shows that you don’t have to stick with the ribose and deoxyribose backbones of RNA and DNA in order to have transmittable, heritable, and evolvable information,” added Eric Kool of Stanford University, California, who also did not participate in the research.

Over the years, scientists have created a range of XNAs, in which the ribose or deoxyribose portions of RNA and DNA are replaced with alternative molecules. For example, threose is used to make TNA, and anhydrohexitol is used to make HNA. These polymers, which do not exist naturally, are generally studied with various biotechnological and therapeutic aims in mind. But some researchers, like Philipp Holliger of the MRC Laboratory of Molecular Biology in Cambridge, UK, think XNAs might also provide insights into the origins of life. They might help to answer questions such as, “why is life based on DNA and RNA, and, if we ever find life beyond earth, is it likely to be based on the same molecule or could there be other possibilities?” Holliger said.

To get at some of these questions, Holliger and his colleagues had to first create enzymes that could replicate XNAs, a necessary first step to evolution. They did this both by randomly mutating and screening existing DNA polymerases for their ability to read XNA, and by an iterative process of selecting polymerase variants with capacities for XNA synthesis. In the end, they had several polymerases that could synthesize six different types of XNA.

To see whether XNAs could evolve, they generated random HNA sequences, then selected for those that could bind to two target molecules. After selection, the HNAs were amplified by the newly designed polymerases and again selected for their ability to bind the targets. Eight rounds of selection later, the HNA sequences were no longer random, as those with a particular target-binding motif became more abundant. Through selection and replication, the HNAs had evolved.

The finding in itself is not surprising, said Kool. “Chemists have been working for 20 years to find new backbones for DNA and the feeling always was that it would be interesting and quite possible that some of them might be replicated one day.” It was, nevertheless, impressive, he added. “The hard part was finding the enzymes that could do it. So the big leap ahead for this paper was finding those enzymes.”

The new polymerases synthesized XNA through rounds of DNA-to-XNA and XNA-to-DNA synthesis. Generating polymerases that can make XNA direct from XNA will be the next step, Holliger said, but it will be a lot harder “because both strands would be foreign to the polymerase.”

Holliger also explained that there was actually a benefit to having a DNA intermediate. “It allowed us to access the whole gamut of technologies that are available for analyzing DNA sequences.” Working with XNAs uniquely, he said, “is like being thrown back to the way molecular biology was in the early 1970s, in that we have to develop all our tools afresh.”

Holliger’s polymerases maybe the first addition to the XNA toolbox but, as more tools are created the potential for XNA biology will grow, said Jack Szostak of Harvard Medical School, who was not involved in the study. “In the longer run, it may be possible to design and build new forms of life that are based on one or more of these non-natural genetic polymers,” he said. That said, “I think it’s too early to say whether such novel life-forms would have any practical applications,” he added.

Regardless of what the future holds, the new polymerases could have applications right away. “We hope to be able to evolve XNA aptamers”—molecules that bind specific targets—“against medically interesting targets,” Holliger said. Scientists are already creating DNA and RNA aptamers, but their use in the body is severely hampered by their susceptibility to naturally occurring nucleases that degrade DNA and RNA. “XNAs are not natural and so are not susceptible to nucleases,” explained Joyce. “These things are bullet-proof.”

Beyond the medical applications of the work, Holliger is finally getting some answers about the basis of life. “The exciting finding of our work is that there really seems to be many possibilities,” he said. “There isn’t anything Goldilocks about DNA or RNA.” Does this mean that life elsewhere in the cosmos is more likely than previously thought? “I would say a cautious yes,” said Holliger.


**CDC to Baby Boomers: Get Tested for Hepatitis C**

Associated Press, (05.18.2012) Mike Stobbe

CDC on Friday announced a proposal to recommend that all people born between 1945 to 1965 get tested for hepatitis C virus. Baby boomers comprise more than 2 million of the estimated 3.2 million Americans thought to have HCV, but many do not know they are infected. CDC officials hope testing all baby boomers will help 800,000 get treated and prevent more than 120,000 deaths.

“The CDC views hepatitis C as an unrecognized health crisis for the country, and we believe the time is now for a bold response,” said Dr. John W. Ward, director of CDC’s Division of Viral Hepatitis.
From 1999 to 2007, US deaths from HCV-related illnesses nearly doubled, recent research found. CDC said more than 15,000 Americans die annually of HCV-related disease, even though two new HCV drugs promise to cure many more patients than was possible before.

Officials think hundreds of thousands of people were infected with HCV each year during the 1970s and 1980s, and many were young adult baby boomers. CDC estimates that 3 percent of boomers test positive for HCV, and most are active, dangerous infections, Ward said.

As many as a quarter of baby boomers with HCV do not remember what put them at risk. The kinds of experiences that might have exposed a person to the blood-borne virus may not ring a bell for many patients or physicians, experts said. Many are diagnosed by happenstance, such as when they donate blood or get tested for a life insurance policy, said Dr. Ryan Ford, an Emory University hepatitis specialist.

The proposed recommendations are expected to become final later this year.

[PNU editor’s note: For more information, visit: http://www.cdc.gov/nchhstp/newsroom/.]

'There’s Evidence that This Really Works and Anything that Works Is Good': Views on the Introduction of Medical Male Circumcision for HIV Prevention in South Africa

AIDS Care Vol. 24; No. 4: P. 496-501, (04..2012) Cecilia Milford; and others

The partial efficacy (40 percent to 60 percent) of surgically conducted medical male circumcision (MMC) in preventing HIV transmission to circumcised men has been demonstrated in three clinical trials. “This research formed part of a larger study exploring the importance of integration of sexual and reproductive health with HIV services,” the authors wrote, noting the objective of eliciting key informants' views on the introduction of MMC for HIV prevention in South Africa.

Semi-structured interviews were used to ask 21 key informants – representing the South African Health Department, local and international non-governmental organizations and universities – about their view on the issue. The interviews were transcribed, and all MMC discussions were coded for analysis using NVivo 8.

Most of the interviewees were knowledgeable about MMC for HIV prevention and indicated that making it available in South Africa was a good idea. Some recommended immediate introduction; others felt MMC should be introduced with caution.

Participants listed numerous factors that should be given consideration. These included culture, the impact of MMC on women, the possibility that behavioral disinhibition might increase risky sexual behavior, and that MMC might become another vertical health service program. Most interviewees felt that MMC should be undertaken in neonates; however, they acknowledged concerns regarding cultural responses to this. MMC implementation recommendations ranged from integrating services at the primary health care level to MMC provision by private medical practitioners.

“In conclusion, MMC is viewed as a key HIV prevention strategy,” the authors wrote. “However, there are numerous factors which could hinder introduction and uptake in South Africa and in the region. It is important to explore and understand these factors and for these to be aligned in the national MMC policy.”

Mayo Clinic study reports increasing incidence of Clostridium difficile infection (C. diff)

Rochester, Minn.—A study presented by Mayo Clinic researchers during Digestive Disease Week 2012 provides clear evidence that the number of people contracting the hard-to-control and treat bacterial infection Clostridium difficile (C. difficile or C. diff) is increasing, and that the infection is commonly contracted outside of the hospital.

"We have seen C.difficile infection as a cause for diarrhea in humans for more than 30 years, and the incidence of infections has been increasing in the last decade," says Sahil Khanna, M.B.B.S., Mayo Clinic Division of Gastroenterology and Hepatology, and lead author of the study. "It has been believed that the typical profile of a person with C. difficile is an older patient, taking antibiotics, while in the hospital. For the first time, we have described a significantly increased incidence of C. difficile in children with diarrhea in a population-based cohort. Importantly, we also found that more than three-quarters of cases of C. difficile in children are being contracted in the community, not in the hospital."

Results of the study showed that the incidence of C.difficile infection (CDI) in children was more than 12 times higher between 2004 and 2009, compared to the period 1991-1997 (32.6 cases per 100,000 vs. 2.6). In addition, 75 percent of cases were "community-acquired," meaning that the patients had not been hospitalized for at least four weeks prior to contracting C. difficile.
C. difficile is an environmental infection, commonly seen on surfaces in the hospital and described to be present in some food sources, including ground beef. Because the infection can be spread from person to person, Mayo Clinic researchers recommend practicing prevention, including:

- Wash hands with soap and water.
- Clean suspected contaminated surfaces with bleach-based solutions.
- Avoid contact with people who are known to have CDI.
- Take extra hygiene precautions if you are living with a person who has CDI or who works in a health care setting where a person might be exposed to patients with CDI.

**New microscope uses rainbow of light to image the flow of individual blood cells**

Non-invasive test promises rapid, pain-free diagnoses without the use of fluorescent dyes

WASHINGTON, May 21—Blood tests convey vital medical information, but the sight of a needle often causes anxiety and results take time. A new device developed by a team of researchers in Israel, however, can reveal much the same information as a traditional blood test in real-time, simply by shining a light through the skin. This optical instrument, no bigger than a breadbox, is able to provide high-resolution images of blood coursing through our veins without the need for harsh and short-lived fluorescent dyes.

"We have invented a new optical microscope that can see individual blood cells as they flow inside our body," says Lior Golan, a graduate student in the biomedical engineering department at the Israel Institute of Technology, or Technion, and one of the authors on a paper describing the device that is published today in the Optical Society's (OSA) open-access journal *Biomedical Optics Express*. By eliminating a long wait-time for blood test results, the new microscope might help spotlight warning signs, like high white blood cell count, before a patient develops severe medical problems. The portability of the device could also enable doctors in rural areas without easy access to medical labs to screen large populations for common blood disorders, Golan notes.

Using the new microscope, the researchers imaged the blood flowing through a vessel in the lower lip of a volunteer. They successfully measured the average diameter of the red and white blood cells and also calculated the percent volume of the different cell types, a key measurement for many medical diagnoses.

The device relies on a technique called spectrally encoded confocal microscopy (SECM), which creates images by splitting a light beam into its constituent colors. The colors are spread out in a line from red to violet. To scan blood cells in motion, a probe is pressed against the skin of a patient and the rainbow-like line of light is directed across a blood vessel near the surface of the skin. As blood cells cross the line they scatter light, which is collected and analyzed. The color of the scattered light carries spatial information, and computer programs interpret the signal over time to create 2-D images of the blood cells.

Currently, other blood-scanning systems with cellular resolution do exist, but they are far less practical, relying on bulky equipment or potentially harmful fluorescent dyes that must be injected into the bloodstream.
"An important feature of the technique is its reliance on reflected light from the flowing cells to form their images, thus avoiding the use of fluorescent dyes that could be toxic," Golan says. "Since the blood cells are in constant motion, their appearance is distinctively different from the static tissue surrounding them." The team's technique also takes advantage of the one-way flow of cells to create a compact probe that can quickly image large numbers of cells while remaining stationary against the skin.

At first, the narrow field of view of the microscope made it difficult for the team to locate suitable capillary vessels to image. To solve this, the researchers added a green LED and camera to the system to provide a wider view in which the blood vessels appeared dark because hemoglobin absorbs green light. "Unfortunately, the green channel does not help in finding the depth of the blood vessel," notes Golan. "Adjusting the imaging depth of the probe for imaging a small capillary is still a challenge we will address in future research."

The researchers are also working on a second generation system with higher penetration depth. The new system might expand the range of possible imaging sites beyond the inside lip, which was selected as a test site since it was rich in blood vessels, has no pigment to block light, and doesn't lose blood flow in trauma patients.

Additional steps include work to miniaturize the system for ease of transport and use. "Currently, the probe is a bench-top laboratory version about the size of a small shoebox," says Golan. "We hope to have a thumb-size prototype within the next year."


### Zooming in On Bacterial Weapons in 3-D: Structure of Bacterial Injection Needles Deciphered at Atomic Resolution

ScienceDaily (May 21, 2012) — The plague, bacterial dysentery, and cholera have one thing in common: These dangerous diseases are caused by bacteria which infect their host using a sophisticated injection apparatus. Through needle-like structures, they release molecular agents into their host cell, thereby evading the immune response. Researchers at the Max Planck Institute for Biophysical Chemistry in Göttingen in cooperation with colleagues at the Max Planck Institute for Infection Biology in Berlin and the University of Washington in Seattle (USA) have now elucidated the structure of such a needle at atomic resolution. Their findings might contribute to drug tailoring and the development of strategies which specifically prevent the infection process.

Hundreds of tiny hollow needles sticking out of the bacterial membrane – it is a treacherous tool that makes pathogens causing plague or cholera so dangerous. Together with a base, embedded in the membrane, these miniature syringes constitute the so-called type III secretion system – an injection apparatus through which the pathogens introduce molecular agents into their host cell. There, these substances manipulate essential metabolic processes and disable the immune defines of the infected cells. The consequences are fatal as the pathogens can now spread within the organism without hindrance. To
date, traditional antibiotics are prescribed to fight the infection. However, as some bacterial strains succeed in developing resistances, researchers worldwide seek to discover more specific drugs.

The exact structure of the 60 to 80 nanometre (60 to 80 millionths of a millimetre) long and about eight nanometre wide needles has so far been unknown. Classical methods such as X-ray crystallography or electron microscopy failed or yielded wrong model structures. Not crystallisable and insoluble, the needle resisted all attempts to decode its atomic structure. Therefore Adam Lange and Stefan Becker at the Max Planck Institute for Biophysical Chemistry together with a team of physicists, biologists and chemists chose a completely novel approach. In cooperation with David Baker at the University of Washington, and Michael Kolbe at the Max Planck Institute for Infection Biology, the scientists successfully combined the production of the needle in the laboratory with solid-state NMR spectroscopy, electron microscopy, and computer modelling. The researchers deciphered the structure of the needle atom by atom and visualised its molecular architecture for the first time in the angstrom range, a resolution of less than a tenth of a millionth of a millimetre.

This required progresses in several fields. “We have made big steps forward concerning sample production as well as solid-state NMR spectroscopy,” says Adam Lange. “Finally, we were also able to use one of the presently most powerful solid-state NMR spectrometers in Christian Griesinger’s NMR-based Structural Biology Department at our Institute.” With 20 tesla, the magnetic field of this 850 megahertz spectrometer is about 400,000 times as strong as that of the earth.

“We were surprised to see how the needles are constructed,” says Lange. As expected, the needles of pathogens causing diseases as diverse as food poisoning, bacterial dysentery, or the plague show striking similarities. However, in contrast to prevailing assumptions, the similarities are found in the inner part of the needles whereas the surface is astonishingly variable. According to the scientist, this variability might be a strategy of the bacteria to evade immune recognition by the host. Changes on the surface of the needle make it difficult for the host’s immune system to recognize the pathogen.

The scientists Lange, Kolbe, Becker, and their Max Planck colleagues Christian Griesinger und Arturo Zychlinsky, have focused on the bacterial injection apparatus for several years. Together with the Federal Institute for Materials Research and Testing they already showed in 2010 how bacteria assemble their miniature syringes. The discovery of their structure in atomic detail not only enables researchers to gain new insights into how these pathogens outwit their host cells, it also offers the prospect to block the syringe assembly and the delivery of the bacterial factors using tailored molecules. Such substances, referred to as anti-infectives, could act more specifically and much earlier during infection than traditional antibiotics. “Thanks to our new technique, we can produce large amounts of needles in the lab. Our aim is now to develop a high-throughput method. This will allow us to search for new agents that prevent the formation of the needle,” explains Stefan Becker.

**Journal Reference:**

**Antibiotic Residues, Some More Than FDA Limits, in Seafood Purchased at US Grocery Stores, Experts Say**
ScienceDaily (May 21, 2012) — After testing farm-raised shrimp samples of international origin researchers at Texas Tech University found evidence of antibiotics—one a suspected human carcinogen—in seafood imported into the United States and purchased from grocery store shelves.

Ron Kendall, director of The Institute of Environmental and Human Health (TIEHH) at Texas Tech, said researchers tested only the muscle tissues consumed by people. When concluded, they found that about 10 percent of the 30 samples tested contained evidence of three antibiotics.

Though the sample sizes were small, he said finding antibiotic residues at all is cause for concern. Todd Anderson, a professor of environmental toxicology, and instrument manager QingSong Cai conducted the shrimp analyses.

In the study, researchers discovered the antibiotic nitrofurazone, a probable carcinogen, in two of the samples purchased in New York—one from a farm in India and the other from Thailand. Both samples were 28 and 29 times higher than the amount allowed by the U.S. Food and Drug Administration (FDA). The limit is 1 part per billion.

"Finding this particular antibiotic is of great interest, especially considering someone could have been eating an item that would have been banned," Kendall said. "Nitrofurazone is a genotoxic substance. It
can affect the DNA of cells and result in genetic toxicity that can possibly result in cancer. You don’t want to ingest it. That’s why the FDA has adopted a zero tolerance stance with it."

The antibiotic chloramphenicol showed up in one sample at 150 times the current FDA required detection limits on prohibited antimicrobial agents in seafood. Trace amounts of enrofloxacin showed up in a sample purchased from a store in Washington, D.C.

"With chloramphenicol, 45 parts per billion is considerably higher than the .3 parts per billion," Kendall said. "It's a very powerful, broad spectrum antibiotic. There is a reason why the U.S. FDA and other countries have set a very low tolerance for this product. You shouldn't be consuming this."

ABC contacted TIEHH to test the shrimp about a year after the U.S. General Accounting Office (GAO) raised serious questions about the safety of imported seafood. In their 51-page report, they cited that half of the seafood imported into the U.S. comes from fish farms, and that these animals, when grown in confined areas, may require antibiotics to treat infections.

The GAO questioned the FDA's oversight program to check for unapproved drug residues in imported seafood samples and called it limited, especially when compared to programs in the European Union.

Samples were purchased from grocery stores in New York, Washington, D.C., Atlanta and Los Angeles.

"These findings were pretty surprising to me," Kendall said. "Considering someone may walk in to a grocery store to buy shrimp to eat, I think that's worth further investigation, and more extensive testing should be done. This was a grab-bag sampling, and we reported what we saw. I don't know yet if it's a greater problem or a lesser problem, but it should be looked into at this point."

Tufts Seeks to Open Infectious Disease Lab

_Tufts Seeks to Open Infectious Disease Lab_  
**Boston Globe**, (05.17.2012)  Kay Lazar

Tufts University recently announced plans to build a $3.5 million biosafety level-three laboratory in an existing facility on the School of Medicine campus. A level-three lab is one in which germs may cause serious or potentially deadly disease from unprotected exposure. About 25-30 people will be authorized to work in the lab; they will investigate new ways to prevent and treat infectious diseases, particularly TB, the university said.

TB is a serious problem both worldwide and in Boston’s Asian community, where the infection rate is 20 times that seen among Caucasians, according to the Boston Public Health Commission. The commission controls permitting for 11 level-three labs in the city’s academic and hospital settings.

The university hopes to begin permitting this month, start construction later this year, and begin operating the lab next year.

Tufts will work closely with its Chinatown neighbors to discuss the whole process, officials said. An informational meeting is planned for Tuesday, May 22, at 6:30 p.m. in Room 114 of the Sackler Center for Medical Education, 145 Harrison Ave., Boston.

"The Arnold 8 Biosafety Laboratory will help us recruit more leading researchers in infectious disease and enable current faculty to expand their research," Dr. John Long, chair of the molecular biology and microbiology department at Tufts, said in a statement.

G8 Leaders Acknowledge Problem Of Counterfeit Drugs In Camp David Declaration

_CQ HealthBeat_ reports on the [G8 Camp David Declaration](http://www.cqhealthbeat.com/), noting that in the statement, G8 leaders acknowledge the problem of counterfeit drugs. "To protect public health and consumer safety, we also commit to exchange information on rogue Internet pharmacy sites in accordance with national law and share best practices on combating counterfeit medical products," is the language in the declaration the leaders of some of the largest nations in the world agreed to over the weekend at the Camp David presidential retreat," the news service writes. According to the Senate Judiciary Committee, "counterfeit drugs cause 100,000 deaths worldwide each year, and are responsible for about $75 billion in annual revenue for criminal operations," _CQ HealthBeat_ notes.

"According to officials at the Pharmaceutical Research and Manufacturers of America (PhRMA), this is the first time the top leaders addressed this issue at one of their meetings," the news service writes. In an interview with _CQ HealthBeat_, Rep. Patrick Meehan (R-Pa.) "said the fact that the G8 leaders mentioned this in their statement 'is an affirmation of the importance of the issue and a recognition of two important impacts: safety as well as the economic implication of the counterfeit activity.'" Meehan added that the G8 statement "is a tremendous boost to our efforts to increase oversight," the news service reports. _CQ HealthBeat_ notes that "the Senate passed by voice vote a bipartisan bill ([S 1886](https://www.congress.gov/bill/112th-congress/senate-bill/1886)) that would
"increas[e] the penalties for trafficking in counterfeit drugs," and Meehan "has introduced a companion measure (HR 3468) in the House that also has bipartisan support" (Bunis, 5/21).

Fake, Substandard Malaria Drugs Threatening Gains Made In Fight Against Disease, NIH Study Warns
"Low-quality and fake anti-malarial drugs flooding into markets in Asia and Africa are driving drug resistance and threatening gains made in the fight against the disease in the past decade, according to a study" conducted by researchers at the National Institutes of Health (NIH) and published Monday in the journal Lancet Infectious Diseases, Reuters reports (Kelland, 5/21). In an analysis of "27 sets of tests of antimalarial drugs purchased in Southeast Asia and Africa between 1999 and 2010," "[a]bout a third of the drug samples from both continents failed," the New York Times writes, noting, "Some were clearly criminal counterfeits, some were expired drugs that had been repackaged and some were poorly made with too little active ingredient" (McNeil, 5/21).

"Fake drugs with no malaria-fighting agents can lead to deaths when patients rely on them, and those containing some active ingredients—but not enough to fully kill all parasites—are also problematic because they promote resistance [in the parasite] that can eventually outsmart medicines and render them useless," the Associated Press writes (Mason, 5/22). "The U.S. researchers from the Fogarty International Center at the [NIH] who carried out the work believe the problem may even be much greater than data suggests," BBC News reports, adding, "'Most cases are probably unreported, reported to the wrong agencies, or kept confidential by pharmaceutical companies,' say the researchers" (Roberts, 5/21). "These findings are a wake-up call demanding a series of interventions to better define and eliminate both criminal production and poor manufacturing of antimalarial drugs,' said Joel Breman" of the NIH, Agence France-Presse writes (5/22).

How one strain of MRSA becomes resistant to last-line antibiotic
Researchers have uncovered what makes one particular strain of methicillin-resistant Staphylococcus aureus (MRSA) so proficient at picking up resistance genes, such as the one that makes it resistant to vancomycin, the last line of defense for hospital-acquired infections. They report their findings in mBio, the online open-access journal of the American Society for Microbiology, on Tuesday May 22.

"MRSA strains are leading causes of hospital-acquired infections in the United States, and clonal cluster 5 (CC5) is the predominant lineage responsible for these infections. Since 2002, there have been 12 cases of vancomycin-resistant S. aureus (VRSA) infection in the United States—all CC5 strains," write the researchers from Harvard, the Massachusetts Eye and Ear Infirmary in Boston and the Broad Institute in Cambridge and other institutions. "Vancomycin is a key last-line bactericidal drug for treating these infections."

The CC5 strain of MRSA has managed to acquire resistance to vancomycin on 12 separate occasions, and although it hasn’t spread widely yet, the risk that MRSA could eventually overwhelm even our last-line drugs is a very serious one. In the study, the researchers sequenced the genomes of all available vancomycin-resistant MRSA strains to find what distinguishes them from other lineages and why CC5 is apparently more adept than other strains at picking up vancomycin resistance.

They report that vancomycin-resistant MRSA strains and other CC5 lineages have some important differences from other types of MRSA, including adaptations that allow them to co-exist with other types of bacteria and may help them take up foreign DNA. They all lack the operon called bsa, for instance, a set of genes that encode a lantibiotic bacteriocin, an antibiotic protein made by bacteria to kill other bacteria. This is important, say the authors, because it enables CC5 to get along well with other bacteria in mixed infections. Instead of killing off competing organisms, CC5 aims to co-exist. This enables it to pick up genes—like the one that encodes vancomycin resistance—from unexpected places. Mixed infections are breeding grounds for antibiotic resistance because they encourage the exchange of genes among very different kinds of organisms.

In roughly the place where these bacteriocin genes are missing is a unique cluster of genes that encode enterotoxins, proteins that attack the human host and, again, could make it easier for mixed populations of bacteria to grow at infection sites.

Finally, CC5 has a mutation in a gene called dprA, which is known to influence the ability to assimilate foreign DNA. The mutation could alter or eliminate the function of dprA in CC5 strains of MRSA, making it amenable to taking up DNA from outside sources.
The sum of all these traits, including the lack of bacteriocin production, the ability to produce enterotoxins, and mutations in the ability to assimilate foreign DNA, is a lineage of S. aureus that is optimized to grow in exactly the types of multi-species infections where gene transfer could occur.

This makes CC5 a dangerous organism in hospitals, say the authors. In hospitals, pathogens are under continuous pressure from antibiotics to survive and evolve, and CC5 isolates appear to be very well adapted to succeed by acquiring new resistances. Frequent use of antibiotics in hospital patients could select for strains like CC5 that have an enhanced ability to co-exist with bacteria that provide genes for antibiotic resistance.

**Harvard team cracks code for new drug resistant superbugs**

Summary: National Institutes of Health-funded scientists have determined the genetic sequences of all 12 available strains of *Staphylococcus aureus* bacteria resistant to vancomycin—an antibiotic of last resort—and have demonstrated that resistance arose independently in each strain after it acquired a specific bit of genetic material called transposon Tn1546. The transposon likely came from vancomycin-resistant *Enterococcus* bacteria that simultaneously infected the patients. The team also identified shared features among the vancomycin-resistant staph strains that may have helped them acquire Tn1546 and evade human immune defenses. Their findings are reported in the May 22 issue of the journal *mBio®.*

Boston (May 22, 2012) — Antibiotic-resistant superbugs, including methicillin resistant Staph. aureus (MRSA), have become household words. Antibiotic resistance threatens health and lives. Schools have been closed, athletic facilities have been scrubbed, and assisted living and day care centers have been examined for transmission of these bacteria. Since 2005, MRSA have killed over 18,000 people a year in the United States alone.

To make matters worse, in 2002 a new MRSA with resistance to even the last-line drug vancomycin (VRSA) appeared. Since the first case in Michigan, there have been at least 11 other well-documented cases in New York, Pennsylvania, Delaware and more in Michigan. Scientists at the Centers for Disease Control, Harvard University and elsewhere have been working to determine the origin of these VRSA, to understand why they have turned up, and to understand the risk of spread. Most VRSA occurred in foot and limb infections of diabetics who are often in and out of health care facilities. Each of these infections is believed to have had multiple bacteria, an MRSA plus a vancomycin resistant bacterium called *Enterococcus* (or VRE). VRE has caused vancomycin resistant hospital-acquired infections since the 1980s.

But there is hope on the horizon. Scientists have now determined the genome sequence for all available VRSA strains. The Harvard-wide Antibiotic Resistance Program is using this information to develop new ways to prevent and treat infection by MRSA, VRSA and VRE. The team identified several new compounds that stop MRSA by hitting new targets, and is currently subjecting these to further tests. This group works closely with partners at the Broad Institute and Harvard’s Microbial Sciences Initiative.

To sequence the genomes, researchers from the National Institutes of Health (NIH)-funded Harvard-wide Antibiotic Resistance Program, headquartered at the Massachusetts Eye and Ear in Boston, assembled an elite international team. Headed by Harvard professor Michael Gilmore, Ph.D., and his associate Veronica Kos, Ph.D., both based at Mass. Eye and Ear, the team included bioinformatics and genomics experts from the Broad Institute of MIT and Harvard, the Institute for Genome Sciences of the University of Maryland, the University of Rochester, and the Wellcome Trust Sanger Center in the UK. They identified features in the genomes that appear to have made it easier for certain MRSA to acquire resistances in mixed infection. Their findings are reported in the May 22 issue of the journal *mBio®*, the American Society of Microbiology's first broad-scope, online-only, open access journal.

("The genome sequence gave us unprecedented insight into what makes these highly resistant bacteria tick. Several things were remarkable," says Gilmore. "Vancomycin resistance repeatedly went into just one tribe of MRSA, so the question became ‘what makes that group special—why did they start getting vancomycin resistance?’"

"What we found was that this group of MRSA has properties that appear to make it more social, so they can live with other bacteria like *Enterococcus*. This would allow those MRSA to more easily pick up new resistances," adds Kos. "The good news is that some of these properties weaken the strain’s ability to colonize, and may be limiting their spread."

Gilmore is the Sir William Osler Professor of Ophthalmology, and also serves in the Department of Microbiology and Immunobiology at Harvard Medical School. Kos is a senior research associate in the
Reactions to HIV drug have autoimmune cause, reports AIDS journal
Research links abacavir hypersensitivity reactions to attacks by body's own immune system

Philadelphia, Pa. (May 22, 2012) – Potentially severe hypersensitivity reactions to the anti-HIV drug abacavir occur through an autoimmune mechanism, resulting from the creation of drug-induced immunogens that are attacked by the body's immune system, according to a study published online by the journal AIDS, official journal of the International AIDS Society. AIDS is published by Lippincott Williams & Wilkins, a part of Wolters Kluwer Health.

The study is the first to explain how hypersensitivity reactions to abacavir develop in genetically predisposed patients—and suggests that similar autoimmune mechanisms might account for other types of drug reactions related to variants in the human leukocyte antigen (HLA) system. The lead author is Dr Michael A. Norcross of the U.S. Food and Drug Administration's Center for Drug Evaluation and Research. The publish-ahead-of-print article is currently available on the AIDS journal homepage and will be available in the July 17, 2012 print edition.

**Abacavir Hypersensitivity Results from 'Drug-Induced Autoimmunity'**

Dr Norcross and colleagues performed a series of laboratory experiments to examine why some patients develop hypersensitivity reactions to the antiretroviral drug abacavir (Ziagen—also included in combination products such as Epzicom and Trizivir). Developing a few weeks after the start of treatment, the reactions cause a wide range of symptoms including fever, rash, nausea, muscle soreness, and shortness of breath.

The reactions have been linked to a gene variant called HLA-B*57:01, found in up to eight percent of people of European descent (lower in other racial/ethnic groups). However, the molecular basis by which people with the HLA-B*57:01 gene develop hypersensitivity reactions to abacavir has been unclear.

In model cells expressing the HLA-B*57:01 gene product, the researchers found that abacavir induced a set of unique changes. **Abacavir exposure led to the formation of new peptide molecules that bound to specific HLA-B*57:01 binding sites.** The result was the creation of new drug-induced immunogens, which could trigger attacks by immune cells.

These findings suggest that abacavir hypersensitivity reactions occur through an autoimmune mechanism—the immune system attacks cells it doesn’t recognize as "self." This is the same basic mechanism that causes autoimmune diseases such as lupus, inflammatory bowel disease, and type 1 diabetes.

This autoimmune mechanism helps to explain why abacavir hypersensitivity reactions can affect such a wide range of different organs and tissues. It also helps in understanding why the reactions clear up promptly when abacavir is stopped, and why more severe reactions can rapidly develop if treatment is restarted.

"Our data support a model of drug-induced autoimmunity as a consequence of abacavir exposure," Dr Norcross and colleagues write. They believe that a similar molecular mechanism could potentially explain other types of drug reactions involving HLA gene variants. It’s also important to identify other factors influencing the development of hypersensitivity, since not all patients with the HLA-B*57:01 gene react to abacavir.

"This study provides important insight into why only certain people show this severe hypersensitivity to this valuable anti-HIV drug," comments Dr J.A. Levy, Editor-in-Chief of AIDS. "The finding represents an example of how approaches to personalized medicine can identify patients who would be sensitive to this side effect of abacavir."

**Newly discovered breast milk antibodies help neutralize HIV**

DURHAM, N.C. – Antibodies that help to stop the HIV virus have been found in breast milk. Researchers at Duke University Medical Center isolated the antibodies from immune cells called B cells in the breast milk of infected mothers in Malawi, and showed that the B cells in breast milk can generate neutralizing antibodies that may inhibit the virus that causes AIDS.
HIV-1 can be transmitted from mother to child via breastfeeding, posing a challenge for safe infant feeding practices in areas of high HIV-1 prevalence. But only one in 10 HIV-infected nursing mothers is known to pass the virus to their infants.

"That is remarkable, because nursing children are exposed multiple times each day during their first year of life," said senior author Sallie Permar, M.D., Ph.D., an assistant professor of pediatrics and infectious diseases at Duke. "We are asking if there is an immune response that protects 90 percent of infants, and could we harness that response to develop immune system prophylaxis (protection) during breastfeeding for mothers infected with HIV-1.

"Our work helped establish that these B cells in breast milk can produce HIV-neutralizing antibodies, so enhancing the response or getting more mucosal B-cells to produce those helpful antibodies would be useful, and this is a possible route to explore for HIV-1 vaccine development," Permar said.

The study was published on May 18 in PLoS One, an open-access journal published by the Public Library of Science.

"This is important work that seeks to understand what a vaccine must do to protect babies from mucosal transmission during breastfeeding," said Barton Haynes, M.D., co-author and a national leader in AIDS/HIV research, director of the Center for HIV/AIDS Vaccine Immunology (CHAVI), as well as director of the Duke Human Vaccine Institute (DHVI). "The antibodies isolated are the first HIV antibodies isolated from breast milk that react with the HIV-1 envelope, and it important to understand how they work to attack HIV-1."

The findings of two different antibodies with HIV-neutralizing properties isolated from breast milk also may help researchers with new investigations into adult-to-adult transmission, in addition to mother-to-child transmission.

Permar said that most HIV-1 transmission occurs at a mucosal site in the body – surfaces lined with epithelial cells, such as the gastrointestinal tract or vaginal tissue. The mucosal compartments all have their own immune system cells.

"We're excited about this finding because the immune cells in mucosal compartments can cross-talk and traffic between compartments," Permar said. "So the antibodies we found in breast milk indicate that these same antibodies are able to be elicited in other tissues."

Interestingly, the Centers for Disease Control in the U.S. recommend against breastfeeding if a mother has HIV-1, because baby formula is a safe alternative for U.S.-born infants. The World Health Organization, however, encourages HIV-infected nursing mothers in resource-poor regions to breastfeed while the mother and/or infant take antiretroviral drugs to prevent the infection in the infant, because without the nutrients and immune factors in mothers' milk, many more infants would die from severe diarrhea and respiratory and other diseases.

At the DHVI and CHAVI, there are many projects aimed at designing neutralizing responses in vaccinated individuals, and for improved vaccines that display specific targets to the immune system before it gets infected, with the idea of eliciting protective responses that fight against HIV transmission.

"Our work will be important in eliminating mother-to-child transmission and getting the types of responses needed for protecting all infants," Permar said.

The study itself wasn't easy to perform, she noted. The samples came from a group of women in Malawi who were recruited by CHAVI for this study.

"Successfully characterizing antibodies from such a fragile medium required global coordination and expertise across multiple fields and is a hopeful testament to the incredible amounts of work and leadership currently under way to fight this devastating disease," said first author James Friedman, a third-year medical student at Duke University School of Medicine. "To be a part of, and to contribute to such a large-scale and important effort is incredibly exciting."

Because of limited availability of the laboratory instrument needed to isolate single, viable immune cells in the region, the samples were not analyzed there. Instead, samples were frozen and transported for analysis. Keeping the breast milk under the right conditions for later thawing and testing of B cells and for isolating antibodies was a challenge, Permar said.
HIV treatment breaks lead to drug resistance in the female genital tract
Michael Carter
Published: 24 May 2012

Antiretroviral treatment interruptions of 48 hours or more are associated with the emergence of resistant strains of HIV in the female genital tract, investigators report in the online edition of the Journal of Acquired Immune Deficiency Syndromes.

The study included 102 women in Kenya who started first-line antiretroviral therapy based on a non-nucleoside reverse transcriptase inhibitor (NNRTI). Drug-resistant virus was detected in the genital tract of five women in the twelve months after treatment was started. Treatment interruptions were the most important risk factor for this outcome.

“We found that ART [antiretroviral therapy] adherence was a key determinant of genital tract resistance and that treatment interruptions of whatever cause lead to a substantial increase in the hazard of detecting genotypic resistance to antiretrovirals in female genital tract secretions,” write the authors.

“Efforts to prevent treatment interruptions by improving program effectiveness, promoting adherence and timely refills, and avoiding the use of more toxic antiretroviral agents could therefore play an important role in reducing transmitted drug resistance.”

First-line HIV therapy often comprises two nucleoside reverse transcriptase inhibitors (NRTIs) combined with an NNRTI. This treatment can have a powerful and durable anti-HIV effect. However, it requires high levels of adherence. Drug-resistant strains of HIV can emerge with poorer adherence. Older drugs in the NNRTI class, nevirapine (Viramune) and efavirenz (Sustiva or Stocrin), have a low barrier to resistance.

Little is currently known about the emergence of drug-resistant virus in the genital tract of women treated with NNRTI-based therapy. This is an important gap in knowledge as drug-resistant virus is potentially transmissible.

Investigators therefore designed a prospective study involving women who started first-line HIV treatment in Mombasa between 2005 and 2008. During the first twelve months after starting therapy viral load was monitored at three-monthly intervals in both plasma and the genital tract. Samples with viral load above 1000 copies/ml were sent for resistance testing. The investigators conducted analysis to see which factors were associated with the emergence of drug-resistant virus in the genital tract.

Overall, the women had high levels of adherence to their antiretroviral therapy. Assessed by pill count, median adherence was 97%. However, there were 40 treatment interruptions. Their median duration was four days. Median pill-count adherence following treatment interruptions was just 83%.

Drug-resistant virus was detected in the blood of nine women (incidence, 10 per 100 person-years) and in the genital secretions of five individuals (incidence, 5.5 per 100 person-years). All five women with resistant HIV in their genital secretions also had resistant virus in their blood.

The investigators’ first set of analysis showed that a number of factors were associated with genital tract resistance. These included treatment interruptions (p = 0.006), pill-count adherence (p = 0.001) and a higher baseline viral load (p = 0.04).

But only treatment interruptions remained significant after controlling for potentially confounding factors. Interruptions were associated with a more than 14-fold increase in the risk of genital tract resistance (aHR = 14.2; 95% CI, 1.3-158.4; p = 0.03).

“The reasons for treatment interruption in this study included both unavoidable discontinuations due to drug toxicity or systemic illness and avoidable interruptions due to late refills, when it is likely that consecutive doses were missed,” note the investigators. “Despite a comprehensive program of adherence support including pre-ART counseling, directly administered therapy during the first month of treatment, a support group, pill boxes and transportation reimbursements, we were unable to prevent these events.”

Transport problems and pharmacy stock-outs have emerged as major barriers to adherence in resource-limited settings. The investigators are concerned that “such barriers may lead to the development of genital tract resistance due to treatment interruptions, suggesting an increased risk for transmission of drug-resistant virus”.

Reference
Kenyan heterosexual couples want a choice of antiretroviral prevention methods
Michael Carter
Published: 23 May 2012
Approximately 40% of HIV-positive people in a stable relationship with an HIV-negative person in Kenya have reservations about starting antiretroviral therapy early for the purposes of prevention, investigators report in the online edition of the Journal of Acquired Immune Deficiency Syndromes.

Willingness to use pre-exposure prophylaxis (PrEP) was high among the HIV-negative partners. However, this finding is likely to have been influenced by the fact that the study involved couples involved in a PrEP study.

The investigators believe that their findings could have implications for the use of HIV treatment in prevention.

“A possible HIV-1 prevention strategy for serodiscordant couples that will utilize both ART [antiretroviral therapy] and PrEP is for the HIV-1-uninfected partner to use PrEP until the HIV-1 infected partner is willing and able to initiate ART,” suggest the authors. “Such a strategy would be cost-effective, provide HIV-1 infected partners an opportunity to decide when to start ART, and may allow a ‘bridge period’ for a few months after the infected partner starts ART, when transmission may still be high because viral load is not yet suppressed.”

Antiretroviral-based strategies are among the most promising new approaches to HIV prevention. Research involving serodiscordant heterosexual couples showed that early antiretroviral therapy reduced the risk of transmission of the virus by 96%.

Some research has also shown that antiretroviral drugs taken by HIV-negative people (PrEP) can reduce their risk of transmission.

Serodiscordant couples are a priority population for the use of HIV treatment. But, before strategies for its use are developed, it is important to understand the couples’ preferences for and concerns about the use of antiretrovirals for this purpose.

Investigators therefore recruited 181 serodiscordant couples in Kenya, enrolled in the Partners PrEP study, to a substudy enquiring about their willingness to use HIV treatment as prevention.

The HIV-positive partners all had a CD4 cell count above 350 cells/mm^3 and were therefore ineligible for antiretroviral therapy according to Kenyan national guidelines. The study was conducted between March and July 2011, before the publication of research showing the efficacy of PrEP in heterosexual couples and of the results from the HTPN 052 study, which showed that early HIV therapy reduced HIV risk by 96% in serodiscordant heterosexual couples.

Both the HIV-negative and HIV-positive partners completed questionnaires.

HIV-negative individuals were asked: “If we find that PrEP works to keep people free from HIV, would you be willing to take PrEP tablets every day for the next five years?”

HIV-infected partners were asked: “Would you be willing to start antiretrovirals before your CD4 count reaches 350 if it would lower your chances of giving HIV to your partner?”

Participants were asked to describe their main concerns about early HIV treatment or PrEP. They were also asked to say which of these strategies they preferred.

Some 69% of HIV-positive men and 58% of HIV-positive woman said that they would be willing to take early treatment for the purposes of prevention.

An overwhelming majority of HIV-negative people (94% of men and 86% of women) expressed a willingness to take PrEP.

When asked to state a preference between the two approaches, 61% of HIV-positive men and 50% of HIV-negative women said they would prefer early HIV therapy.

A majority of HIV-negative participants expressed a preference for PrEP (57% of men and 56% of women).

In just over a quarter of couples (26%), both members preferred to have the HIV-negative partner take PrEP and in 22% of couples both members preferred early antiretroviral therapy for the infected partner.

Among HIV-positive participants, the primary concerns about early treatment for prevention were side-effects (51%), stigma (21%), pill burden (19%) and fears about resistance (18%).

A total of 14 HIV-negative people were unwilling to use PrEP. Their primary concerns were the duration of treatment (6/14), taking treatment when they were not sick (3/14), and side-effects (3/14).

“In our study, not all couples would be willing to use ART prior to the HIV-1 infected partner having clinical symptoms and a perceived need for initiation; PrEP could be a suitable alternative for these...
couples,” conclude the authors. “As antiretroviral-based HIV-1 prevention strategies are incorporated into prevention policies and programs, it will be important to understand and accommodate couples’ preferences and willingness to use antiretroviral-based HIV-1 prevention.”

Reference

NICE says sperm washing is no safer than effective treatment and timed intercourse
Roger Pebody
Published: 22 May 2012
Draft UK guidance on fertility treatment says that sperm washing may no longer be necessary for couples where the man has HIV and the woman does not. As long as the man is on effective antiretroviral treatment and unprotected sex is limited to days when his partner is ovulating, “sperm washing may not further reduce the risk of infection.”

On the other hand, the guidance does not support the use of pre-exposure prophylaxis (PrEP) by the HIV-negative partner.

The National Institute for Health and Clinical Excellence (NICE) is an influential body which issues recommendations to the NHS about the most effective and cost-effective treatments to provide. Their draft guidance on fertility treatments – an update to a document previously issued in 2004 – was issued today and is open for consultation.

As in the previous version, people with HIV are not excluded from access to fertility treatments, such as intrauterine insemination (IUI) or in vitro fertilisation (IVF). Moreover, the authors have removed a previous recommendation that the implications of the parent’s HIV infection for the child’s welfare “should be taken into account”.

The writing group reviewed in detail the scientific evidence for different methods that a couple could use to become pregnant, where the man has HIV and the woman does not. Previous guidance recommended sperm washing, but the experts also looked at the evidence for effective antiretroviral treatment and for pre-exposure prophylaxis.

“The evidence showed that whilst sperm washing did not appear to completely eliminate the virus in the semen on the basis of post-wash testing of prepared semen, the procedure appears to be very effective in reducing viral transmission in that no cases of seroconversion of the woman or the baby has been documented,” they found.

On the other hand, sperm washing has the disadvantage of reducing the likelihood of pregnancy occurring.

Moreover, the writing group identified effective HIV treatment as an alternative “which is equally effective, less invasive and more cost effective”.

They propose a criteria, similar to that of the ‘Swiss statement’, to determine whether unprotected vaginal intercourse would be an appropriate way to conceive. All the following conditions should be met:

- Unprotected intercourse is limited to the time of ovulation.
- The man is complying with highly active antiretroviral therapy (HAART).
- The man has a plasma viral load of less than 50 copies/ml.
- There are no other sexually transmitted infections.

The authors insist that their recommendation is limited to the situation of a heterosexual couple wishing to conceive and who limit unprotected sex to days when the female partner is fertile (ovulating). The authors have not provided guidance that is relevant to the risk of HIV transmission in other circumstances: “The context of this recommendation should not be extrapolated away from this remit,” they say.

Should the man have problems with adherence to antiretroviral therapy or were his plasma viral load to be detectable, the guidance recommends that his seminal viral load be tested. If HIV is undetectable in semen, doctors should inform the couple that the risk of HIV transmission during timed unprotected intercourse is “negligible”.

In situations other than these, sperm washing should still be recommended.

Moreover, the document acknowledges that some couples may still be anxious about the risk of HIV transmission during unprotected intercourse when the male partner is on effective treatment. In such a case, sperm washing would still be considered.

In terms of pre-exposure prophylaxis (PrEP), the experts looked at whether, for a couple in which the HIV-positive man was on effective treatment, there would be an additional benefit for his HIV-negative
female partner in taking PrEP. They found only two studies in peer-reviewed journals that shed light on the question and that this evidence did not support the use of PrEP.

Consultation is open until 3 July.

Further information
Further information on the consultation can be found here. For details of the evidence on sperm washing examined by NICE, see pages 105 to 122 of the "full guidance" document (pdf).

‘Gay cure’ therapist loses appeal against the British Association of Counselling and Psychotherapy
Lesley Pilkington, a psychotherapist who was found guilty of ‘professional malpractice’ for using the techniques of ‘conversion therapy’ (a bogus form of treatment which is supposed to make gay people become straight) has lost her appeal against the British Association for Counselling and Psychotherapy (BACP). Mrs Pilkington was found guilty of malpractice last year after trying to convert a gay client to heterosexuality, with the BACP describing her practice as ‘negligent’, ‘dogmatic’ and ‘unprofessional’. The British Humanist Association (BHA) welcomes the BACP’s decision.

The complaint against Mrs Pilkington which started this case was made by the award-winning journalist Patrick Strudwick, who was investigating therapists who claim to be able to ‘treat’ homosexuality. Mr Strudwick, who is gay, received two counselling sessions from Mrs Pilkington in 2009, in which she used the techniques of ‘conversion therapy’ (also known as ‘reparative therapy’) in an attempt to make him become heterosexual. The treatment, which also involved praying to God to make Mr. Strudwick straight, failed. As well as attempting to ‘cure’ Mr Strudwick’s homosexuality, Mrs Pilkington also suggested that he had been sexually abused as a child.

The BACP said that ‘the appeal panel is unanimous that Mrs. Pilkington failed to exercise reasonable care and skill and was thus negligent.’ The panel also said it was ‘entirely wrong’ for Mrs Pilkington to suggest that Mr Strudwick had been sexually abused as a child, and that this ‘falls below the standard to be expected of a reasonably competent practitioner.’ The BACP have suspended Mrs Pilkington’s accreditation, and have ordered her to submit a report between 4 and 12 months from now, in which she will have to demonstrate that she has changed her practice to meet the BACP’s requirements. Mr Strudwick said that ‘I am delighted that the BACP has upheld their original decision. Mrs Pilkington’s therapeutic practices have been held up to scrutiny and found to be fundamentally flawed.’ He also said that ‘this case sets a vital precedent. I urge anyone involved in this harmful practice to take note of this case and desist. Love needs no cure.’

Pavan Dhaliwal, the BHA Head of Public Affairs, commented, ‘treatments which attempt to “cure” homosexuality are morally objectionable because they carry the implication that homosexuality is a disease. They also lack any foundation in scientific fact, having been condemned by the UK Council for Psychotherapy, the British Medical Association and the Royal College of Psychiatrists, as well as in the recent judgement by the BACP. These so-called treatments can also be extremely harmful, especially when they are applied to vulnerable individuals.’

Therapies which claim to be able to ‘cure’ homosexuality now lie completely discredited. In addition to the case of Mrs Pilkington in the UK, there is also the case of Dr Robert Spitzer in the US. Dr Spitzer, a highly influential figure in modern psychiatry, claimed in a study in 2001 that homosexuality could be cured, but he has recently retracted his views, admitting that his study was ‘fatally flawed’. The BHA now calls on all who have supported anti-gay ‘conversion therapies’, such as the former Archbishop of Canterbury Lord Carey, the former Bishop of Rochester Rt Rev Michael Nazir-Ali, and the lobby group Christian Concern (all of whom supported Lesley Pilkington) to retract their views.

African monkey meat that could be behind the next HIV
Deep in Cameroon’s rainforests, poachers are killing primates for food. Evan Williams reports from Yokadouma on a practice that could create a pandemic
Evan Williams
Friday, 25 May 2012
Deep in the rainforest of south-east Cameroon, the voices of the men rang through the trees. "Where are the white people?" they shouted. The men, who begin to surround us, are poachers, who make their money from the illegal slaughter of gorillas and chimpanzees. They disperse but make it known that they are not keen for their activities to be reported; the trade they ply could not only wipe out critically endangered species but, scientists are now warning, could also create the next pandemic of a deadly virus in humans.
Eighty per cent of the meat eaten in Cameroon is killed in the wild and is known as "bushmeat". The nation's favoured dishes are gorilla, chimpanzee or monkey because of their succulent and tender flesh. According to one estimate, up to 3,000 gorillas are slaughtered in southern Cameroon every year to supply an illicit but pervasive commercial demand for ape meat.

"Everyone is eating it," said one game warden. "If they have money they will buy gorilla or chimp to eat."

Frankie, a poacher in the southern Dja Wildlife reserve who gave a fake name, said he is involved in the trade because he can earn good money from it, charging around £60 per adult gorilla killed. "I have to make a living," he said. "Women come from the market and order a gorilla or a chimp and I go and kill them."

Cameroon's south-eastern rainforests are also home to the Baka – traditional forest hunters who have the legal right to hunt wild animals, with the exception of great apes.

Felix Biango, a Baka elder, said the group used to hunt gorilla every few weeks to feed his village, Ayene, but has stopped since Cameroon outlawed the practice 10 years ago. However, he says that every week, three or four people come from the cities to ask the group to help them to hunt wild animals, such as gorillas and chimpanzees.

While the Baka no longer hunt primates for themselves, Mr Biango says that they still kill gorillas for the commercial trade and will eat the meat if they find the animals already dead.

Though Cameroonians have eaten primate meat for years, recent health scares have begun to raise fears about the safety of the meat. "In the village of Bakaklion our brothers found a dead gorilla in the forest," Mr Biango said. "They took it back to the village and ate the meat. Almost immediately, everyone died – 25 men, women and children – the only person who didn't was a woman who didn't eat the meat."

Three-quarters of all new human viruses are known to come from animals, and some scientists believe humans are particularly susceptible to those carried by apes. The human immunodeficiency virus (HIV) is now widely believed to have originated in chimps. Apes are known to host other potentially deadly viruses, such as ebola, anthrax, yellow fever and other potential viruses yet to be discovered.

Babila Tafon, head vet at the primate sanctuary Ape Action Africa (AAA), in Mefou, just outside the capital Yaounde, believes the incident that Biango describes could have been caused by an outbreak of ebola, but cannot be sure because no tests were carried out.

AAA now cares for 22 gorillas and more than one hundred chimps – all orphans of the bushmeat trade.

Mr Tafon tests the blood of all apes arriving at the sanctuary. He says he has recently detected a new virus in the apes – simian foamy virus, which is closely related to HIV. "A recent survey confirmed this is now in humans, especially in some of those who are hunters and cutting up the apes in the south-east of the country," he said.

Viruses are often transferred from ape to human through a bite, scratch or the blood of a dead ape getting into an open wound. There is a lower risk from eating cooked or smoked primates, but it is not completely safe.

Bushmeat is not only a concern for Cameroonians. Each year, an estimated 11,000 tons of bushmeat is illegally smuggled in to the UK, mainly from West Africa, and is known to include some ape meat.

The transfer of viruses from ape to man is a primary concern for the international virology research and referral base run by the Pasteur Centre in Yaounde. Each week, it screens more than 500 blood samples for all manner of viruses, and alerts major international medical research centres if it finds an unfamiliar strain.

Professor Dominique Baudon, the director of the Cameroon centre, says he is concerned that the bushmeat trade is a major gateway for animal viruses to enter humans worldwide, due to the export trade. He says that the deeper poachers go in to the forest, and the more that primates are consumed, the more exposed people become to new unknown viruses and the more potential there is for the viruses to mutate into potentially aggressive forms. At the Ape Action Africa sanctuary, Rachel Hogan, who came to Cameroon from Birmingham 11 years ago, and her team focus on the last of Cameroon's great apes.

It is not known exactly how many gorillas remain in the wild in Cameroon. Conservationists estimates there may be only a few thousand Western Lowland Gorillas left, which are being gradually forced in to smaller groups by hunting and the destruction of their habitat by logging. In the west of the country, there are only 250 Cross River Gorillas left.

Hunting does not just affect adult apes. One hunter said a baby gorilla had screamed so much for its dead mother, killed for her meat, that he eventually killed it to stop the noise.
Most of the gorillas and chimps Ms Hogan and her team look after are babies who have witnessed the murder of their parents. She says they are often suffering from terrible wounds and even trauma when they arrive at the sanctuary. "They grieve just like humans," she says. "We have had them where they will just sit rocking, grinding their teeth and they don't respond to anything. You have to be able to win back their trust."

Ms Hogan says the apes can even die after the trauma. "They'll stop eating, they won't respond to anything... [They] decide whether they live or die. It's like watching a clock wind down."

The increasing number of rescued apes is putting pressure on the sanctuary. A group of eight gorillas in the wild, protected by one dominant male, needs 16 square kilometres to roam in to live comfortably.

The sanctuary says there is nowhere in the vast tropical rainforest of Cameroon that the apes can safely be returned to the wild. "If this continues there might not be any wild populations of gorillas left," says Ms Hogan.

'Unreported World: The Monkey Business', Channel 4, 7.30pm tonight

Out of Africa: How HIV was born
Aids, the worst pandemic of modern times which has claimed over 30 million lives, is thought to have begun in the rainforest of west central Africa as a result of the bush meat trade. For decades, perhaps centuries, wild chimpanzees carrying the Simian Deficiency Virus (SIV) have come into contact with humans who have caught and eaten them. SIV is genetically similar to HIV and, occasionally, when a chimp scratched or bit a hunter, the virus will have been passed on and may have mutated into HIV. In the distant past, when communications were poor, outbreaks of HIV would not have spread beyond the forest. But in the latter part of the last century, as the commercial exploitation of Africa gathered pace, the opportunities for viral spread increased.

Today, the scale of the slaughter is immense. The Washington-based Bush Meat Crisis Task Force estimates that up to five million tons of wild animals are being "harvested" in the Congo Basin every year – the equivalent of 10 million cattle. The trade was initially driven by hunger – it was a cheap source of food – but has burgeoned with increased logging of the forests and growing demand.

Now, it is international, extending the threat beyond the continent's boundaries. Scientists have warned that Britain is at risk from an outbreak caused by the lethal Ebola or Marburg viruses contained in illegal imports of bush meat from Africa.

The size of the imports is unknown, but one 2010 study estimated that five tons of the meat per week were being smuggled in personal baggage via Roissy-Charles de Gaulle airport in Paris, France. Gorilla and chimpanzee meat is said to be on offer to African communities in Hackney and Brixton at hundreds of pounds per kilogram.

Jeremy Laurance

Gilead Files European Marketing Application for Boosting Agent Cobicistat

FOSTER CITY, Calif. — (BUSINESS WIRE) — May. 23, 2012 — Gilead Sciences, Inc. (Nasdaq: GILD) announced today that the Marketing Authorisation Application (MAA) for cobicistat, submitted on April 26, 2012, has been validated by the European Medicines Agency (EMA). Cobicistat is Gilead’s pharmacoenhancing or “boosting” agent that increases blood levels of certain commercially available protease inhibitors, including atazanavir and darunavir, in order to enable once-daily dosing. Currently, ritonavir is the only agent used to boost HIV therapy. Review of the MAA for cobicistat will be conducted under the centralized licensing procedure, which, when finalized, provides one marketing authorization in all 27 member states of the European Union (EU).

"With today's EMA validation, we're hopeful that we may soon be able to offer an important new boosting option for patients who rely on protease inhibitors as part of their HIV therapy," said Norbert Bischofberger, PhD, Executive Vice President, Research and Development and Chief Scientific Officer, Gilead Sciences.

The MAA for cobicistat is supported by pharmacokinetic data demonstrating that cobicistat boosts atazanavir and darunavir exposure similar to ritonavir, and by 48-week data from a pivotal Phase 3 study (Study 114) in which cobicistat met its primary objective of non-inferiority to ritonavir, when both agents were administered with a background regimen of atazanavir plus Truvada® (emtricitabine and tenofovir disoproxil fumarate). Topline results from the study were announced in December 2011, and complete data will be presented at an upcoming medical meeting.

Gilead plans to submit an application for marketing approval of cobicistat to the U.S. Food and Drug Administration (FDA) in the third quarter of 2012. Cobicistat is a component of Gilead’s investigational
Quad single tablet regimen, which also contains elvitegravir, emtricitabine and tenofovir disoproxil fumarate. Cobicistat enables once-daily dosing of elvitegravir within the Quad.

In June 2011, Gilead announced an agreement with Janssen R&D Ireland for the development of a fixed-dose combination of cobicistat and darunavir. Subject to regulatory approval, Janssen will be responsible for the formulation, manufacturing, registration, distribution and commercialization of the cobicistat and darunavir fixed-dose combination worldwide. Additionally, in October 2011, Gilead announced an agreement with Bristol-Myers Squibb to develop a fixed-dose combination of cobicistat and atazanavir. Bristol-Myers Squibb will be responsible for the formulation, manufacturing, development, registration, distribution and commercialization of the atazanavir and cobicistat fixed-dose combination worldwide.

**About Cobicistat**
Cobicistat is Gilead’s proprietary mechanism-based inhibitor of cytochrome P450 3A (CYP3A), an enzyme that metabolizes drugs in the body. Unlike ritonavir, cobicistat acts only as a pharmacoenhancer and has no antiviral activity.

Cobicistat, elvitegravir and the Quad are investigational products and their safety and efficacy have not yet been established.

**About Gilead Sciences**
Gilead Sciences is a biopharmaceutical company that discovers, develops and commercializes innovative therapeutics in areas of unmet medical need. The company’s mission is to advance the care of patients suffering from life-threatening diseases worldwide. Headquartered in Foster City, California, Gilead has operations in North America, Europe and Asia Pacific.

**Forward-Looking Statement**
This press release includes forward-looking statements, within the meaning of the Private Securities Litigation Reform Act of 1995, that are subject to risks, uncertainties and other factors, including the risk that EMA and other regulatory agencies may not approve cobicistat, any combination products containing cobicistat, elvitegravir or the Quad, and that any marketing approvals, if granted, may have significant limitations on their use. In addition, even if approved, Gilead may not be able to successfully commercialize these products, and may make a strategic decision to discontinue their development if, for example, the market for the products fails to materialize as expected. Further, Gilead may be unable to submit its New Drug Application for cobicistat to FDA in the currently anticipated timelines. These risks, uncertainties and other factors could cause actual results to differ materially from those referred to in the forward-looking statements. The reader is cautioned not to rely on these forward-looking statements. These and other risks are described in detail in Gilead’s Quarterly Report on Form 10-Q for the quarter ended March 31, 2012, as filed with the U.S. Securities and Exchange Commission. All forward-looking statements are based on information currently available to Gilead, and Gilead assumes no obligation to update any such forward-looking statements.

**Muslim Women, Religious Leaders Being Enlisted In Global Campaign To Eradicate Polio**
"The last three countries where polio is still paralyzing children—Afghanistan, Pakistan and Nigeria—said on Thursday that they have enlisted Muslim women and religious leaders to allay fears of vaccination and wipe out the disease," Reuters reports. According to Shahnaz Wazir Ali, a special assistant to Pakistan's Prime Minister who is in charge of the polio eradication campaign, more than 20 leading Islamic scholars "have signed an endorsement of the polio eradication program, which is being used to persuade Pakistani parents" to allow their children to be vaccinated, the news agency writes. In Nigeria, the Federation of Muslim Women's Associations is backing a polio immunization campaign there, Reuters notes. "It is not the first time that the world has come tantalizingly close to wiping out the crippling disease," the news agency writes. "'We're so close, there is no time for complacency,' Dr. Christopher Elias, head of global development at the [Bill & Melinda Gates Foundation], a major donor, told Reuters in Geneva," Reuters adds (Nebehay, 5/24).

**Editorial, Opinion Piece Examine Future Of World Health Organization**
As the World Health Assembly draws to a close in Geneva this week, and Margaret Chan accepts her appointment to a second five-year term as director-general of the World Health Organization (WHO), an editorial and an opinion piece examine the future of the U.N. health agency. Summaries of these pieces appear below.
Richard Horton, *Lancet*: "In WHO's annual World Health Statistics, released last week, the agency chose, correctly, to present a picture of change," Horton, editor-in-chief of the Lancet, writes, adding, "WHO must be a science-led and data-driven organization," led by scientists. He continues, "WHO's greatest challenge [is] to focus on a few priority initiatives, and to realign resources to support those priorities." Horton says the WHO should focus on "three programmatic pillars"—health of the people of Africa, women's health, and non-communicable diseases—that "must be part of an inspirational vision ... that has gradually been forming: universal health care in an era of sustainable development." He concludes, "The agency has 12 months to put 'reform' behind it and to embark on a phase of vigorous leadership and strategic renewal. It is at next year's World Health Assembly that another report card needs to be written—this time not just for health, but for WHO itself" (5/26).

Devi Sridhar, Lawrence Gostin, and Derek Yach, *Foreign Affairs*: "After 15 years of heralded progress on pandemic preparedness, tuberculosis control, tobacco regulation, and health metrics, the World Health Organization faces confusion over its future," Sridhar, a lecturer in global health politics at Oxford University; Gostin, a professor of law at Georgetown University; and Yach, senior vice president of global health and agricultural policy at PepsiCo and former executive director of the WHO, write. "The most serious examples [are] the WHO's inability to address non-communicable disease (NCD) prevention globally, to improve access to health systems, and to set global priorities in health," they argue. "To be effective, the WHO needs to assert the importance of health in decision-making at the national level" and "to be at the table when global trade and financial decisions are negotiated," they write, adding, "Stronger diplomatic abilities adapted from the trade and finance regimes, in addition to a well-articulated case for linkage to major global debates on sustainable development, human rights, and security, will earn the WHO its right in settings where health can truly flourish" (5/24).

**Polio Eradication Must Not Fail**

"[P]eople everywhere have a stake in eradicating polio, as we have stamped out smallpox," a Bloomberg View editorial states, adding, "Immunizing the last unvaccinated children on the planet is an expensive and complex undertaking, and worth it in the long run." The editorial notes, "If polio transmission could be stopped by 2015, the net benefit from reduced treatment costs and productivity gains through 2035 would be $40 billion to $50 billion, according to a 2010 study."

"Thanks to the efforts of the Global Polio Eradication Initiative—which links national governments to the World Health Organization, the U.S. Centers for Disease Control and Prevention, UNICEF, Rotary International and the Bill & Melinda Gates Foundation—progress has been tremendous," the editorial writes, noting, "Polio cases dropped from 350,000 in 1988 to 60 so far this year. In the same period, endemic countries fell from 125 to three." However, the editors continue, "[j]ust as the eradicators were closing in, the job's completion has been threatened by a $1 billion funding gap in the global initiative's $2.19 billion budget." The editorial notes the "coalition has adopted an emergency plan" that prioritizes vaccination in the three remaining polio-endemic countries and concludes, "The world has come too close and the stakes are too high for polio eradication to fail" (5/24).
Structure of Human Protein Critical for Silencing Genes Solved

ScienceDaily (May 25, 2012) — In a study published in the journal *Cell* on May 24, Cold Spring Harbor Laboratory (CSHL) scientists describe the three-dimensional atomic structure of a human protein bound to a piece of RNA that "guides" the protein's ability to silence genes. The protein, Argonaute-2, is a key player in RNA interference (RNAi), a powerful cellular phenomenon that has important roles in diverse biological processes, including an organism's development.

"Detailed knowledge of the structure of human Argonaute-2 and the way it interacts with its RNA guides will greatly improve our understanding of its biological mechanism of action," says CSHL Professor and HHMI Investigator Leemor Joshua-Tor, Ph.D., the study's leader. "Such precise structural information of the human Argonaute bound to an important RNA guide could potentially aid both basic research to understand the function of genes and also advance the development of RNAi as a therapeutic strategy in clinical settings."

Upon the activation of a gene within a cell, the gene's DNA is copied into a messenger RNA (mRNA) "transcript." The instructions encoded within this transcript are then used as a blueprint by the cell's protein synthesis machinery to generate a working protein. The gene is "silenced" or prevented from giving rise to the protein, however, when an Argonaute-2 protein that is bound to a small piece of "guide" RNA—either a short-interfering RNA or a microRNA—intercepts the mRNA molecule. The guide RNA, whose nucleotide sequence matches that of the target mRNA, acts as a homing device that helps the Argonaute-2 protein zero in on the mRNA target.

A few years ago, Joshua-Tor collaborated with CSHL Professor and HHMI Investigator Gregory Hannon, Ph.D., who is also a co-author in this study, to show that Argonaute proteins, which are made up of different domains or parts, act like a pair of molecular scissors that slice up target mRNAs, thus preventing proteins from being made and enforcing the silencing of their genes. The discovery of the Argonautes' "slicer" activity stemmed in part from solving the crystal structure of an Argonaute protein from *Pyrococcus furiosus*, an archebacterium that thrives in extremely high temperatures. "But we still know nothing about the biological functions or mechanisms of action of archebacterial Argonautes," says Joshua-Tor. "We therefore next focused on solving the structures of Argonautes from higher organisms such as mammals, in which Argonaute functions and target recognition are well documented."

Joshua-Tor's team and other research groups subsequently determined the atomic structures of individual parts of Argonaute proteins from higher organisms. While these studies revealed several important details—for example, the interaction between two parts of the Argonaute protein, called the PAZ and Mid domains, with the two ends of guide RNAs—Joshua-Tor's goal was to solve the structure of the entire human Argonaute protein in complex with a single human guide RNA.
Overcoming a complicated series of technical challenges, her team has achieved this goal by analyzing the structure of a full-length human Argonaute-2 protein bound to a small RNA called miR-20a, which is known to play a role in cancer development. Although Argonautes from higher organisms diverged from their archebacterial cousins more than three billion years ago, the team's analysis shows remarkable similarity between the two structures, especially in the regions that are important for target recognition and slicing activity.

"Our structure shows that the guide RNA, which is anchored at both ends by the PAZ and Mid domains, kinks and twists its way through the structure of the entire protein, making several points of contact within each domain and with the linker loops that join them," explains Joshua-Tor. "The guide RNA thus acts like a backbone that rigidly locks together the otherwise flexible Argonaute protein and gives it stability."

The researchers speculate that the path threaded through the Argonaute by the guide RNAs could have evolved to maximize mutual stability, in turn making the protein-RNA complexes long-lived. This long life is critical for many biological processes that are mediated by Argonautes. "This is also the kind of information that might help us to design better synthetic guide RNAs for therapeutic use," explains Joshua-Tor. "It will also be useful to researchers who are trying to find more precise ways of blocking Argonaute activity."

Journal Reference:

Irritable Bowel Syndrome Clearly Linked to Gut Bacteria
ScienceDaily (May 25, 2012) — An overgrowth of bacteria in the gut has been definitively linked to Irritable Bowel Syndrome in the results of a new Cedars-Sinai study which used cultures from the small intestine. This is the first study to use this "gold standard" method of connecting bacteria to the cause of the disease that affects an estimated 30 million people in the United States.

Previous studies have indicated that bacteria play a role in the disease, including breath tests detecting methane—a byproduct of bacterial fermentation in the gut. This study was the first to make the link using bacterial cultures.

The study, in the current issue of Digestive Diseases and Sciences, examined samples of patients' small bowel cultures to confirm the presence of small intestinal bacterial overgrowth—or SIBO—in more than 320 subjects. In patients with IBS, more than a third also were diagnosed with small intestine bacterial overgrowth, compared to fewer than 10 percent of those without the disorder. Of those with diarrhea-predominant IBS, 60 percent also had bacterial overgrowth.

"While we found compelling evidence in the past that bacterial overgrowth is a contributing cause of IBS, making this link through bacterial cultures is the gold standard of diagnosis," said Mark Pimentel, MD, director of the Cedars-Sinai GI Motility Program and an author of the study. "This clear evidence of the role bacteria play in the disease underscores our clinical trial findings, which show that antibiotics are a successful treatment for IBS."

IBS is the most common gastrointestinal disorder in the U.S., affecting an estimated 30 million people. Patients with this condition suffer symptoms that can include painful bloating, constipation, diarrhea or an alternating pattern of both. Many patients try to avoid social interactions because they are embarrassed by their symptoms. Pimentel has led clinical trials that have shown rifaximin, a targeted antibiotic absorbed only in the gut, is an effective treatment for patients with IBS.

"In the past, treatments for IBS have always focused on trying to alleviate the symptoms," said Pimentel, who first bucked standard medical thought more than a decade ago when he suggested bacteria played a significant role in the disease. "Patients who take rifaximin experience relief of their symptoms even after they stop taking the medication. This new study confirms what our findings with the antibiotic and our previous studies always led us to believe: Bacteria are key contributors to the cause of IBS."

The study is a collaboration with researchers at Sismanogleion General Hospital in Athens, Greece, and at the University of Athens.

Journal Reference:
Gene Kim, Fnu Deepinder, Walter Morales, Laura Hwang, Stacy Weitsman, Christopher Chang, Robert Gunsalus, Mark Pimentel. Methanobrevibacter smithii Is the Predominant Methanogen in Patients with Constipation-Predominant IBS and Methane on Breath. Digestive Diseases and Sciences, 2012; DOI: 10.1007/s10620-012-2197-1
Girl brides abducted as fabled HIV cure
By Justine Lang and Robyn Curnow, CNN
KwaCele, South Africa (CNN)--The landscape of the rural Eastern Cape in South Africa has a haunting beauty. A myriad of round turquoise huts scatter across the land in a series of endless villages.

Yet these villages are also home to a terrible and devastating traditional practice that destroys children's lives and tears families apart.

In these villages, girls as young as 12 are kidnapped by older men and forced to 'marry.' It is accepted as part of the Xhosa people's culture. It has continued unabated for decades.

Ukuthwala, which translates as 'to pick up' or 'to take,' is used to justify the abduction of girls. In many cases the parents have given their consent in exchange for a bride price.

But a concerted campaign to educate these isolated communities of the illegality of under-aged sex and abduction appears to be paying off.

Nombasa Gxuluwe, born in the Eastern Cape, is a field worker for the World Aids Campaign (WAC), and has dedicated herself to trying to end what is essentially the buying and selling of brides, many of them still children.

Nombasa and many other organizations have spent hours talking to the men in the villages, trying to make them understand that the rules are different now.

For many, like Timothy Nyawuse, there was simply no awareness that what was being done was wrong.

"We apologize for that as we did not know we were breaking the law," he tells CNN.

Complicating the matter is a chilling, modern belief, as Nombasa explains: "There is a myth that if you sleep with a young girl who is a virgin and as a man you are HIV positive then HIV can be cured. That is why they are focusing on these young girls."

Nombasa said many of the male abductors are older men, widowed by HIV. They then look for a younger "virgin bride" and invariably end up infecting them too.

The tradition has its roots in arranged marriages where parents or village elders have the final say on who girls should marry.

And when men started taking younger and younger wives, elders in villages with no electricity or running water did not realize the modern world would see.

In the documentary, "Ukuthwala – Stolen Innocence," made by WAC, a girl living in the village of Lusikisiki in the Eastern Cape tells her story of being a victim of this practice.

"The lady from next door called me and asked me if I wanted to get married. I said no. She said if I refused they would take me by force and beat me up.

"The next night the lady came to my house and took me to the river. There were seven people waiting there. They made me go with them to the house where the man lived. I couldn’t believe this was happening to me. That I was getting married.

"There was this old man in the room and he told me, "I paid cattle for you and whether you like it or not you are my wife."

"He picked me up and put me on the bed and undressed me. He also got undressed and tried to force himself on me. I fought him but he pushed me down and forced my legs open. That’s when he slept with me."

For those who have the courage to escape their illegal 'marriages' there is a place of refuge. The Palmerton Care Centre is housed in the grounds of a Methodist Church, in Lusikisiki.

It is here that social workers first counsel the young girls and then help them integrate back into the community.

It is no easy journey. Many have had years out of school. Some are infected with HIV. Others are no longer wanted back by their families, accused of bringing shame on them for not staying in the marriage.

Nombasa said: "They see them as rebellious, uncontrollable, because they are not obeying the rules of the parents, of the community."

The National Prosecuting Authority in South Africa is making a concerted effort in the villages surrounding KwaCele to show that such practices are illegal. Eleven men in the past year have been charged with abduction and under-age sex. None of the cases have yet reached court.

Even more promising, Nombasa said that since December 2011 there has not been a new case reported. She said: "It looks like we are winning."
HIV vaccine carries its own adjuvant into clinical trials
May 24, 2012 | By Suzanne Elvidge
Following its "allowed to proceed" notice, the NIH-funded HIV Vaccine Trials Network (HVTN) has started enrollment of GeoVax's second-generation HIV vaccine. The trial will include 48 people at four sites in the U.S., 40 receiving the vaccine at increasing doses and 8 as controls, and will check the safety of the vaccine, as well as look out for an immune response.

The DNA-based vaccine expresses the same HIV proteins as the first-generation vaccine, which is currently in Phase IIa, but carries its own adjuvant in the form of DNA expressing granulocyte-macrophage colony-stimulating factor (GM-CSF).

"We are extremely pleased the HVTN is conducting the trial with the adjuvanted vaccine. They have substantial experience with our unadjuvanted vaccine and possess appropriate expertise for this first human trial of our GM-CSF co-expressing vaccine that has shown such good promise in preclinical studies," Robert McNally, Ph.D., president and CEO of GeoVax, said.

The vaccine is given in two steps—two shots of the HIV/GM-CSF DNA vaccine to stimulate the immune system and trigger antibodies against the virus, followed by two booster shots of MVA, a recombinant poxvirus expressing HIV proteins. In animal studies, the vaccine protected 5 out of 7 animals from infection. If this study is successful, the company will move this form of the vaccine into Phase IIa/IIb trials.

T cells 'hunt' parasites like animal predators seek prey, a Penn Vet-Penn Physics study reveals
PHILADELPHIA — By pairing an intimate knowledge of immune-system function with a deep understanding of statistical physics, a cross-disciplinary team at the University of Pennsylvania has arrived at a surprising finding: T cells use a movement strategy to track down parasites that is similar to strategies that predators such as monkeys, sharks and blue-fin tuna use to hunt their prey.

With this new insight into immune-cell movement patterns, scientists will be able to create more accurate models of immune-system function, which may, in turn, inform novel approaches to combat diseases from cancer to HIV/AIDS to arthritis.

The research involved a unique collaboration between the laboratories of senior authors Christopher Hunter, professor and chair of the Pathobiology Department in Penn's School of Veterinary Medicine, and Andrea Liu, the Hepburn Professor of Physics in the Department of Physics and Astronomy. Penn Vet postdoctoral researcher Tajie Harris and physics graduate student Edward Banigan also played leading roles in the research.

The study, which will be published in the journal Nature, was conducted in mice infected with the parasite Toxoplasma gondii. This single-celled pathogen is a common cause of infection in humans and animals; as much as a third of the world's population has a dormant form of this infection present in the brain. However, in immunocompromised individuals, such as those with HIV/AIDS or undergoing organ transplantation, this infection can have serious consequences, including brain inflammation and even death.

Earlier work had shown that T cells — a key immune-cell type — are central in preventing disease caused by T. gondii. In the new study, the Penn researchers used the infected mice as a natural model system to learn how the movement of T cells in the brain affects the body's ability to control this infection.

Among immunologists, it's widely believed that the movement of immune cells is governed in part by signaling proteins called chemokines. The Penn-led team demonstrated that a specific chemokine, CXCL10, and its receptor were abundantly produced in the brains of T. gondii-infected mice. When CXCL10 was blocked, mice had fewer T cells, a greater parasite burden and actively reproducing parasites.

Next the researchers sought to pinpoint the exact movement patterns of individual T cells in living tissue from T. gondii-infected mice. This was possible with multi-photon imaging, a technique that relies on a refined yet powerful microscope that can display living tissues in three dimensions in real time. Using this approach, the team found that CXCL10 appeared to play a role in the speed at which T cells are able to search for and control infection.

To the extent that immunologists had considered T-cell movement patterns at all, many assumed that they moved in a highly directed fashion to find infected cells. But when the researchers analyzed the movement of T cells, they found their data did not match what would be expected: the T cells showed no directed motion.

That's where the statistical physics expertise of Liu and Banigan came in.
"We looked at a much more complete way to quantify these tracks and found that the standard model didn’t fit at all," Liu said. "After some work we managed to find a model that did fit the tracks beautifully."

"The model that finally led us down the right path," Banigan said, "had a strong signature of something really interesting," a model known as a Lévy walk.

This "walk," or a mathematically characterized path, tends to have many short "steps" and occasional long "runs." The model was not fully consistent with the data, however.

"Rather, I had to look at variations on the Lévy walk model," Banigan said, because the researchers also observed that the T cells paused between steps and runs. Like the movements of the cells, the pauses were usually short but occasionally long.

Hunter likened the model to a strategy a person might employ to find misplaced keys in the house.

"When you lose your keys, how do you go about looking for them? You look in one place for a while, then move to another place and look there," he said.

"What that leads to is a much more efficient way of finding things," Liu said.

And, indeed, when the team generalized the Lévy strategy against other strategies, they confirmed that the Lévy walk was a more efficient technique to find rare targets. That makes sense for T cells, which have to locate sparsely distributed parasites in a sea of mostly normal tissue.

Interestingly, T cells are not alone in employing a Lévy-type strategy to find their targets. Several animal predators move in a similar way—with many short-distance movements interspersed with occasional longer-distance moves—to find their prey. The strategy seems particularly common among marine predators, including tuna, sharks, zooplankton, sea turtles and penguins, though terrestrial species like spider monkeys and honeybees may use the same approach to locate rare resources.

This parallel with animal predators also makes sense because parasites, like prey species, have evolved to evade detection.

"Many pathogens know how to hide, so T cells are not able to move directly to their target," Hunter said. "The T cell actually needs to go into an area and then see if there’s anything there."

The model is also relevant to cancer and other immune-mediated diseases, Hunter noted. "Instead of looking for a parasite, these T cells could be looking for a cancer cell," he said. By knowing what controls T cell movement, "you might be able to devise strategies to make the T cells more efficient at finding those cells."

On the physics side, while the Lévy-walk model is not new, the fact that T cells pause in between their steps or runs is something that hadn’t been recognized before when mapping the paths in other contexts.

"From a physics point of view, to have runs and pauses is a new model," Liu said. "Biological phenomena can illustrate what we wouldn’t have thought about otherwise."

The Penn collaborators are working to plot the tracks of other cell types and credit their unique partnership for their discovery.

"We’ve said all along that this study could only happen because [our physics colleagues] had such a great expertise and we had our own separate expertise," Tajie Harris said. "They took a chance working with us, and it turned out to be something really rewarding."

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**Antiretroviral treatment for preventing HIV infection: an evidence review for physicians**

While immediate postexposure treatment for suspected HIV is critical, pre-exposure preventive treatment is a newer method that may be effective for people in high-risk groups, states a review of evidence published in CMAJ (Canadian Medical Association Journal).

"Although postexposure prophylaxis has a long history of success, newer methods such as pre-exposure prophylaxis and earlier treatment in the course of infection ("treatment as prevention") are being implemented with some success," writes Dr. Isaac Bogoch, Harvard Medical School and the Division of Infectious Diseases, Massachusetts General Hospital, Boston, with coauthors.

Several recent large randomized controlled trials have added to knowledge about pre-exposure prevention and early initiation of antiretroviral therapy. To provide physicians with current pharmacologic prevention methods, researchers from Massachusetts General Hospital, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts and Sunnybrook Health Sciences, Toronto conducted a review of literature from January 1990 to April 2012.

HIV is transmitted mainly through unprotected sex, contaminated needles and from mother to baby, although the latter transmission was not part of the review.
After assessing with a detailed history whether a person has been exposed to HIV, postexposure treatment (prophylaxis) should begin as soon as possible or within 72 hours and be continued for 28 days. If the patient is in a low-risk situation but not completely without risk, the physician and patient can decide upon the risks of transmission and whether to treat prophylactically. Current practice recommends a two-drug regimen of tenofovir with emtricitabine and a third drug in people with high-risk exposure.

"Evidence for quickly starting prophylaxis and a four-week duration of therapy stem from macaque models of transmission, in which starting prophylaxis later and shorter durations of therapy resulted in higher rates of HIV seroconversion [development of antibodies against HIV],” write the authors.

For high-risk populations, such as men who have sex with men, intravenous drug users and women in areas with a high prevalence of HIV, pre-exposure prophylaxis has been shown to prevent HIV infection before being exposed to the virus. For example, one recent trial that involved 900 women from a region with high HIV prevalence showed a 39% reduction in HIV infection rates after application of a topical vaginal microbicide 12 hours before and after sex.

"All pre-exposure prophylaxis interventions should be considered one part of a more comprehensive plan for preventing the spread of HIV infection, including standard counseling on safer sexual practices and condom use, testing for and treating other sexually transmitted infections and, in select circumstances, male circumcision and needle exchange programs,” state the authors.

"Whereas pre-exposure prophylaxis may be reserved for people with the highest risk of exposure, the trend of treating HIV at higher CD4 T cell counts earlier in infection will likely show the most promise as a pharmacologic strategy for preventing transmission of the virus,” the authors conclude. They note that while pre-exposure prophylaxis is promising, there are unanswered questions, such as which groups would benefit most, the possibility of drug resistance and others. Several large-scale trials are underway to determine effectiveness of early treatment.

U of M study finds titan cells protect Cryptococcus

MINNEAPOLIS/ST. PAUL (MAY 28, 2012)— Giant cells called "titan cells" protect the fungus Cryptococcus neoformans during infection, according to two University of Minnesota researchers. Kirsten Nielsen, Ph.D., an assistant professor in the department of microbiology, and recent Ph.D. recipient Laura Okagaki believe their discovery could help develop new ways to fight infections caused by Cryptococcus.

The findings will be published in the June issue of the journal Eukaryotic Cell. The study was funded by the National Institutes of Health and the University of Minnesota's Medical School.

Cryptococcus, a fungus frequently found in dust and dirt, is responsible for the deaths of more than 650,000 AIDS patients worldwide each year. It is also a potentially deadly concern among chemotherapy and organ transplant patients. Currently, Cryptococcus causes more annual deaths in sub-Saharan Africa than tuberculosis.

"While most healthy individuals are resistant to Cryptococcus infections, the fungus can cause deadly disease for those with already weak immune systems,” said Dr. Nielsen.

When inhaled, Cryptococcus can cause an infection in the lungs. This infection can spread to the brain and result in meningitis, an often-deadly inflammation of the brain and spine.

Nielsen and Okagaki found that titan cells, or Cryptococcus cells ten to twenty times the size of a normal cell, are too large to be destroyed by the body's immune system.

Researchers also found the presence of titan cells can protect all Cryptococcus cells in the area, even the normal sized Cryptococcus cells.

"This tells us that titan cell formation is an important aspect of the interaction between the human/host and the organism that allows Cryptococcus to cause disease,” said Nielsen. "This information will help us find new ways to treat Cryptococcus infections that are very difficult to treat with currently available drugs.”

Powerful New Approach to Attack Flu Virus

ScienceDaily (May 27, 2012) — An international research team has manufactured a new protein that can combat deadly flu epidemics.

The paper, featured on the cover of the current issue of Nature Biotechnology, demonstrates ways to use manufactured genes as antivirals, which disable key functions of the flu virus, said Tim Whitehead, assistant professor of chemical engineering and materials science at Michigan State University.
"Our most potent design has proven effective on the vulnerable sites on many pandemic influenza viruses, including several H1N1 (Spanish flu, Swine flu) and H5N1 (Avian flu) subtypes," said Whitehead, the paper's co-lead author. "These new therapeutics are urgently needed, so we were especially pleased to see that it neutralizes H1N1 viruses with potency."

From its earlier research, the team used computer-aided design to engineer proteins that targeted vulnerable sites on the highly adaptable virus. From there, researchers optimized their designer proteins by comprehensively mapping the mutations that gave the proteins a strong advantage when attacking the viruses' targeted areas.

The team improved its proteins through a process called "DNA deep sequencing." This allowed Whitehead and his colleagues to simultaneously sequence millions of variants of their manufactured proteins, identify and keep the beneficial mutations and optimize the proteins' performance.

"By taking only the best mutations, we can reprogram our proteins to burrow into viruses at key locations and render them harmless," he said. "Our work demonstrates a new approach to construct therapeutic proteins, which we hope will spur development of new protein drugs by the biopharmaceutical industry."

This research also laid the groundwork for future treatments of all flu viruses as well as other diseases such as smallpox, Whitehead added.

**Journal Reference:**

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**Garlic Constituent Blocks Biofilm Formation, Could Benefit Cystic Fibrosis Patients and Others**

ScienceDaily (May 27, 2012) — *E Pluribus Unum*, the de facto motto of the United States, could just as well apply to biofilm-forming bacteria. Bacterial biofilms are far more resistant than individual bacteria to the armories of antibiotics we have devised to combat them. Now Tim Holm Jakobsen and Michael Givskov of the University of Copenhagen, and their many collaborators have pinpointed a constituent of garlic that attacks a key step in the development of biofilms, in an effort they hope may offer help in particular for patients with cystic fibrosis.

The research is published in the May 2012 issue of *Antimicrobial Agents and Chemotherapy*.

In earlier work, Givskov and his colleagues showed that "crude extracts of garlic inhibit the expression of a large number of genes that are controlled by bacterial quorum sensing [communication among bacterial cells involved in biofilm development], and that extracts promote a rapid clearing of pulmonary *Pseudomonas aeruginosa* infection in mice," he says. "These findings encouraged us to identify and assess the efficacy of the pure active compound."

That compound turned out to be ajoene, the major constituent of a multitude of sulfur-containing compounds produced when garlic is crushed, says Jakobsen. The team then showed in *P. aeruginosa* that ajoene inhibits expression of 11 genes that are controlled by quorum sensing. "These key genes are regarded as crucial for the ability of *P. aeruginosa* to cause disease," he says.

"We also found ajoene to reduce the production of rhamnolipid, a compound that shields the biofilm bacteria from the white blood cells that otherwise would destroy bacteria, and that by combining ajoene with the antibiotic tobramycin, it was possible to kill over 90 percent of bacteria living in a biofilm," says Jakobsen.

"Our study is part of a series of comprehensive investigations of natural compounds targeting bacterial quorum sensing systems, and it further strengthens previous proof of concept research we conducted on the potential of compounds which block communication among pathogen cells in contrast to simply killing bacteria, as conventional antibiotics do," says Jakobsen. Such alternative approaches "may postpone or minimize development of antibiotic resistance," he adds.

Jakobsen says the garlic project grew out of a major donation from the German Cystic Fibrosis Association. "In CF patients, *P. aeruginosa* infection leads to bronchieciasis, pulmonary fibrosis, respiratory failure, and death," he says. "Despite intensive antibiotic treatment, CF patients have a life expectancy of about 40 years, and the main cause of death in CF patients remains complications associated with [this infection]." Jakobsen’s team and the German CF Association have patented the action of ajoene against biofilms, and are seeking a pharmaceutical partner to develop antimicrobial drugs based on ajoene.
Jakobsen notes that garlic has been used medicinally “for thousands of years.” Garlic not only has antibacterial properties; it has anti-viral, anti-fungal, and anti-protozoal properties as well, and it has beneficial effects on the cardiovascular and immune systems, as well, he says.

**Journal Reference:**

**Experimental Vaccine Elicits Robust Response Against Both HIV and Tuberculosis, Study Suggests**
ScienceDaily (May 21, 2012) — Clinician researchers in China have developed a vaccine that acts simultaneously against HIV-1 and *M. tuberculosis* (Mtb). An estimated 14 million people worldwide are coinfected with the two pathogens. The research is published in the May 2012 issue of *Clinical and Vaccine Immunology.*

The vaccine is composed of antigens from both pathogens. The team, led by Sidong Xiong of Fudan University, Shanghai, incorporated four Mtb epitopes (the part of an antigen that is recognized by the immune system) into a backbone composed of HIV-1 p24 protein, a protein that is known to produce protective immunity against HIV-1. The logic of this construction: many epitopes are short peptides, with poor immunogenicity unless they are introduced into a carrier protein—which in this case was the p24 protein.

The vaccine induced cellular immune responses to both pathogens, in which immune system cells including macrophages search out and destroy pathogens; and humoral immune response against HIV-1, in which the immune system produces antibodies against the pathogen. The vaccine was tested in a mouse model.

Tuberculosis is one of the leading causes of death worldwide; third, after hepatitis C and then HIV/AIDS among infectious diseases, according to the World Health Organization (WHO). An estimated 2 billion—28 percent of the world’s population—are infected with *M. tuberculosis*, but most of these infections are latent. However, HIV infection is the strongest risk factor for the progression of latent tuberculosis infection to active TB. And TB is the direct cause of death in about one quarter of all deaths among people with HIV/AIDS, according to the WHO.

**Journal Reference:**

**HIV prevalence beginning to fall in South African children**
Carole Leach-Lemens
Published: 29 May 2012
HIV prevalence fell sharply among children admitted to one of South Africa’s largest hospitals in 2009 and 2010, but remained high at 19.3%, researchers from Chris Hani Baragwanath (CHB) hospital in Soweto report in the advance online edition of the *Journal of Acquired Immune Deficiency Syndromes.*

In the 15 years preceding 2009, HIV prevalence among children admitted to the hospital had remained remarkably constant, peaking at 31.7% in 2005. This indicated the extremely high rate of vertical HIV transmission in South Africa prior to the implementation of up-to-date interventions to reduce it.

However, the persistently high prevalence indicates that – despite improvements in the efficacy of interventions to prevent mother-to-child transmission – huge numbers of pregnant women with HIV in South Africa were still failing to receive effective treatment and care that could prevent their child from acquiring HIV.


While pneumonia was the most common cause of death throughout, deaths attributable to tuberculosis (TB) steadily increased from 18 to 26.3% and 44% in 2005, 2007 and 2010-11, respectively. TB continues to be an important co-infection in HIV-infected children.
These results show an encouraging trend, but with close to one-fifth of the approximate 6000 admissions in 2010/2011 to the CHB paediatric wards HIV-related, improved treatment coverage – as well as prevention of TB disease – remains critical.

In 2009, South Africa had an estimated 330,000 HIV-infected children (over 13% of children infected worldwide) and as many as one in three deaths among children under the age of five is estimated to be HIV-related.

Tracking HIV prevalence of children admitted to hospital has been used as an indication of the effect of HIV on health services for children. At CHB hospital this has been evaluated on and off for about 20 years. Twenty-three children were diagnosed with HIV between May 1989 and April 1990. From 1990 to 1996 HIV-related paediatric admissions increased from 1% to close to 30%, reflecting the rapid increase of HIV infection among pregnant women. During this same period, in-hospital paediatric HIV-related death rates increased by 42%.

ART provision for adults and children was introduced in 2004 by the South African Department of Health. While uptake has been slow, South Africa now has the largest ART programme in the world, with an estimated 54% paediatric ART coverage in 2010. Evaluation of the effectiveness in 2010 of the national PMTCT programme showed that 31.4% of infants were HIV-exposed, while the MTCT rate was 3.5% in these infants at 4 to 8 weeks of age.

In light of these programming improvements, the authors chose to describe the effect on HIV prevalence and in-patient death rates among children admitted to CHB hospital. The hospital serves a population of 1.4 million in Soweto, Johannesburg, in the Gauteng province of South Africa. Close to 6000 children, aged up to 15 years, are admitted every year.

Methods among the surveillance studies differed. For the most recent – from 1 August 2010 to 31 January 2011 – children were enrolled prospectively from one of four general paediatric wards.

From 1 October to 31 December 2007, a cross-sectional retrospective review of all children admitted to all four wards was undertaken.

The 2005 study was part of a larger sentinel surveillance study to monitor the effect of HIV on health services in Gauteng Province. Information was collected for all patients admitted in four hospitals over a 4 to 6 week period in April and May 2005. CHB hospital was one of the sites and children were enrolled from all four wards.

From 1 July to 31 December 1996, children under the age of five admitted to one ward at CHB hospital were enrolled.

The results show an encouraging trend: both HIV-related paediatric hospital admissions and overall death rates decreased. Such progress, note the authors, is reflective of improved PMTCT programmes and ART coverage.

In addition, over the time period, new vaccines were introduced into the South African immunisation programme against influenza, pneumonia and diarrhoea. While less effective in HIV-infected children, they have shown efficacy in reducing the burden of these diseases.

The authors suggest increased death and disease due to TB may reflect an increase in TB prevalence, caused by increased household exposure or the increased risk for TB immune reconstitution inflammatory syndrome (IRIS) in children taking antiretroviral therapy in more recent times. While there are improved tools for TB diagnosis, diagnostic methods for paediatric TB have not changed, so this cannot explain the rise in TB-related deaths in later time periods.

The authors stress that “efforts to prevent TB disease and death should focus on the use of isoniazid preventive therapy, early diagnosis and treatment of TB”.

Death rates declined among HIV-infected children. While there was no significant change in death rates among HIV-negative children, they were consistently lower than in their HIV-infected counterparts: 11.2 (65/565) and 24% (43/179) in 2005; 6 (91/1510) and 12% (53/440) in 2007; and 4.2 (18/429) and 12/3% in 2010-11, respectively.

Children under six months are especially vulnerable to HIV-related death. This study showed a decrease both in death rates and absolute numbers admitted among this age group in 2010-11: 66.7 (18/27, 2005), 70 (28/40, 2007) and 44.4% (4/9, 2010-2011). This finding leads the authors to “cautiously anticipate a reduction in infant and under five mortality rates...to attain MDG4 of a two thirds reduction in under five mortality by 2015”.

The median age of children with HIV admitted to hospital increased in 2010-11: from 9.13 months (IQR: 3.6-28.8) in 2005 and 10 months (IQR: 3.0-44.5, p>0.10) in 2007 to 18 months (6.2-69.8, p=0.048) in 2010-11. The increase in median age is explained, the authors note, by the continued expansion of PMTCT programmes resulting in fewer infants becoming infected.
Limitations include the absence of a uniform surveillance system at the hospital – so all surveys used different methodologies, making any direct comparisons difficult.

Budgetary constraints meant fewer staff were available to get informed consent from caregivers in 2010-11, resulting in the smallest sample size of the studies. The authors did not believe this resulted in bias.

CHB hospital is a large, urban, academic hospital in a well-resourced province so these findings may not be generalisable to lesser-resourced or rural settings.

The authors conclude that “even though results from the PMTCT programme are reassuring, HIV is a preventable condition in children, and most cases should be successfully prevented... A high index of suspicion for HIV-infection should be maintained and routine HIV screening of all children presenting at health services should increase in order to diagnose all infants and older children. With continued effort, South Africa can regain some ground in attaining the MDG4 target and substantially reduce new HIV infections and HIV-related deaths among children.”

Reference

**HIV-Positive Women in Argentina Mainly Infected by Stable Partners**

By Marcela Valente

**BUENOS AIRES, May 28, 2012 (IPS) –**The immense majority of women diagnosed with HIV in Argentina in the last two years were infected through unprotected sex with their stable partners, a new report says.

"In some cases, they are couple who have been together for years," Maria Eugenia Gilligan, an activist with the Argentine Network of Women Living with HIV, told IPS. "The age range has even expanded, and we are finding more and more women over 60."

This national organisation and the Buenos Aires Network of People Living with HIV jointly surveyed 465 women in that situation around the country for the "Study of Recently Diagnosed Women".

The women interviewed were all diagnosed since Jan. 1, 2009. The aim was to find out in what circumstances they were infected. Gilligan said many of the women were "uninformed."

The sample included women between the ages of 17 and 70, although 51 percent were 25 to 39. Around 70 percent had reached but not necessarily completed secondary school, and a few had university or other tertiary level education.

The report to which IPS had access has not yet been officially released, but the preliminary results were presented on the International Day of Action for Women's Health, celebrated Monday May 28. The survey described the living conditions of the respondents. For example, it reported that more than half of them live in crowded homes, 70 percent have no social security coverage, and only 46 percent work outside the home.

The study was carried out by the Gino Germani Research Institute of the University of Buenos Aires, and the Centre of Population Studies, with the backing of the Health Ministry and multilateral organisations like U.N. Women and the Joint United Nations Programme on HIV/AIDS (UNAIDS).

The chief conclusions are that 92 percent of women living with HIV were infected by means of unprotected sexual relations, while 73 percent said they were infected within a stable relationship.

The results partly coincide with Health Ministry statistics which indicate that there are 130,000 people living with HIV in this country of 40 million people, where the main channel of transmission is unprotected sex.

"We noted that since 2008 there is less public information available and there are more uninformed women. Specific campaigns are needed, and counselling and advice are failing. Although a lot is being done, there is much more to do," Gilligan said.

For 60 percent of those surveyed, the diagnosis was "totally unexpected." One 51-year-old woman said that after being faithful to the man she lived with for 11 years, she couldn’t believe she had been infected. Official statistics suggest that up to half of all people living with HIV in this country do not know they are infected.

"We almost always see the same thing. The women didn’t know (their male partners) had the virus," said Gilligan, who added that violence "is one factor that increases the vulnerability of women by making them reluctant to demand the use of condoms, as a precautionary measure."

She said a majority of the women living with HIV had suffered physical and/or sexual abuse from a young age.
"It’s not that they don’t insist on condom use because they are crazy," Gilligan said. "The problem is that many of them cannot negotiate the issue with their partners, out of fear of violence, so they use other methods of birth control."

The study also found that over 44 percent of the women had experienced conflict or tension with their partners at some point over the use of condoms.

Most of the women interviewed said they discovered they were HIV-positive by chance: when they were pregnant, during a routine check-up, or in pre-surgery tests. Only 10 percent had gone in for testing after finding out that their partners were living with HIV.

The report also discusses what happens once a woman has found out that she tests positive for the AIDS virus. It points to shortcomings in terms of confidentiality, and in counselling to help women deal with the situation.

Some women, for example, face "hostile situations" when they are told they test positive for HIV, the report says. It also mentions cases in which a family member is informed even before the woman herself, or in which she is told of her HIV-positive status in front of others, such as doctors, nurses or relatives.

The personal accounts also show that there are women who leave the medical clinic or hospital without fully understanding the results of the test. "They told me it was ‘reactive’, but I didn’t know if that meant positive or not," one of the respondents said.

State Allows Pharmacies to Offer More Vaccines


Massachusetts currently allows pharmacists to administer annual flu shots, but a new state health policy will expand that authority to include giving vaccinations for hepatitis A and B; human papillomavirus; measles, mumps and rubella; tetanus, diphtheria, and whooping cough; shingles; pneumonia; chickenpox; and meningitis.

Kevin Cranston, director of the Department of Public Health (DPH) Bureau of Infectious Disease, said the move by regulators is designed to make vaccination more convenient and cost-effective. An office visit to or a prescription from a primary care provider is not necessary, which in turn lowers the work load of physicians, he said.

David Johnson, executive vice president of the Massachusetts Pharmacists Association, said consumers who face transportation and time constraints likely will benefit most from the policy. But Dr. Lynda Young, president of the Massachusetts Medical Society, worries it will make the task of tracking what vaccines a patient has had and when more difficult for physicians.

A 2010 Massachusetts law established, but did not fund, a state vaccine registry. DPH has used federal money to launch pilot registries at several sites; officials said last fall that a statewide rollout was planned for 2012.

Massachusetts has often led the nation in childhood immunization rates, but adult rates have lagged. Under the policy, finalized last month, pharmacists must undergo training that meets state standards for vaccine administration.

A Comparison of Sexual Behavior Patterns Among Men Who Have Sex with Men and Heterosexual Men and Women

Journal of Acquired Immune Deficiency Syndromes Vol. 60; No. 1: P. 83-90, (05.01.2012) Sara Nelson Glick, PhD, MPH; and others

MSM have higher HIV and other STI rates than do women and heterosexual men—an elevated risk that persists across age groups and reflects biological and behavioral factors. However, few direct comparisons of sexual behavior patterns have been done between these populations.

The study authors compared sexual behavior patterns of MSM and male and female heterosexuals ages 18-39 using four population-based random digit dialing surveys. MSM data estimates came from a 1996-1998 survey in four US cities and from two Seattle surveys (2003 and 2006); a 2003-2004 Seattle survey provided data about heterosexual men and women.

Compared with heterosexuals, MSM had an earlier sexual debut, and they reported longer cumulative lifetime periods of new partner acquisition and a more gradual decline in new partnership formation with age. Among MSM, 86 percent of those ages 18-24 and 72 percent of those ages 35-39 formed a new partnership during the past year, compared with 56 percent of heterosexual men and 34 percent of women ages 18-24, and 21 percent and 10 percent, respectively, at 35-39. In addition, MSM were more likely to choose partners >5 years older and two to three times as likely as heterosexuals to report
concurrent partnerships. MSM reported more consistent condom use during anal sex than was reported during vaginal sex by heterosexuals.

“MSM have longer periods of partnership acquisition, a higher prevalence of partnership concurrency, and more age diassortative mixing than heterosexuals,” the authors concluded. “These factors likely help to explain higher HIV/[STI] rates among MSM, despite higher levels of condom use.”

**Widespread Cholera Vaccination Needed In Haiti While Improvements Made To Water, Sanitation Systems**

"As the world's worst outbreak of cholera continues to ravage Haiti, international donors have averted their gaze," a *Washington Post editorial* writes. The editorial notes that a "pilot project to vaccinate Haitians against the disease ... reached only one percent of the population, with no immediate prospect of expansion," and "[i]f the 100 or so cholera treatment centers that sprung up around the country after the disease was detected 19 months ago, fewer than a third remain." The solution to the epidemic is "equally well known and costly," the editorial states, adding, "Haiti needs modern water and sanitation infrastructure, an undertaking that might cost $1 billion. But while donors tend to respond generously to emergencies, such as the earthquake that devastated Haiti in early 2010, they lose interest in long-term fixes of the sort that would deal decisively with cholera."

"Groups representing thousands of Haitian cholera victims have demanded millions of dollars of reparations from the United Nations," citing allegations that U.N. peacekeepers introduced the disease to the island nation, but if the international body raises funds, the money "would be more profitably spent on a much more aggressive cholera vaccination program," the Washington Post states. Noting that approximately $40 million would be needed for a large-scale vaccination program, the editorial says, "International health organizations dragged their feet on vaccines, worrying they might be too expensive or difficult to administer. They preferred a systemic infrastructure fix." But "[t]hat's simply indefensible," according to the editorial, which concludes, "It may take many years to provide adequate water and sanitation systems in Haiti, but a two-dose vaccine that costs $4 per person can be manufactured right now. Granted, there will be logistical hurdles to overcome ... But to do nothing in the interim is immoral" (5/26).

**NIH scientists identify new HIV-inhibiting protein**

**Potential role in HIV treatment and prevention under study**

Scientists have identified a new HIV-suppressing protein in the blood of people infected with the virus. In laboratory studies, the protein, called CXCL4 or PF-4, binds to HIV such that it cannot attach to or enter a human cell. The research was led by Paolo Lusso, M.D., Ph.D., chief of the Section of Viral Pathogenesis in the Laboratory of Immunoregulation at the National Institute of Allergy and Infectious Diseases (NIAID), part of NIH.

CXCL4 belongs to a family of molecules called chemokines that help regulate the movement of immune cells around the body. In the mid-1990s, four chemokines—three discovered by Dr. Lusso, Robert Gallo, M.D., and their colleagues—were found in laboratory experiments to function as HIV inhibitors. These chemokines as well as CXCL4 may regulate the level of virus replication in infected individuals and thus the pace at which HIV disease progresses.

According to Dr. Lusso, the site where CXCL4 binds to the outer coat of HIV seems to be different from other known vulnerable sites targeted by HIV-blocking antibodies and drugs. His team is working with scientists at the NIAID Vaccine Research Center to define the atomic-level crystal structure of this binding site, which potentially may play a role in the future development of HIV treatments or vaccines.

CXCL4 differs from the other four major HIV-suppressive chemokines in several respects. The other four chemokines inhibit HIV infection by binding to either one of two cell receptors—called CCR5 and CXCR4—used by the virus to attach to and enter immune cells, whereas CXCL4 binds directly to the outer surface of the virus. While the other chemokines bind to forms of HIV that use either the CCR5 or the CXCR4 receptor, CXCL4 can bind to and block infection by a wide variety of HIV strains, no matter what their receptor specificity. Finally, while the other chemokines are made primarily by immune cells, CXCL4 is made by platelets, the blood cells involved in clotting.

Dr. Lusso and his colleagues are pursuing further research to better understand CXCL4’s role in HIV disease and to determine whether the chemokine has a protective effect not only in laboratory studies, but also in people.
Why Swine Flu Virus Is Developing Drug Resistance
ScienceDaily (May 29, 2012) — Computer chips of a type more commonly found in games consoles have been used by scientists at the University of Bristol to reveal how the flu virus resists anti-flu drugs such as Relenza and Tamiflu.

Professor Adrian Mulholland and Dr Christopher Woods from Bristol's School of Chemistry, together with colleagues in Thailand, used graphics processing units (GPUs) to simulate the molecular processes that take place when these drugs are used to treat the H1N1-2009 strain of influenza—commonly known as 'swine flu'.

Their results, published May 29 in Biochemistry, provide new insight that could lead to the development of the next generation of antiviral treatments for flu.

H1N1-2009 is a new, highly adaptive virus derived from different gene segments of swine, avian, and human influenza. Within a few months of its appearance in early 2009, the H1N1-2009 strain caused the first flu pandemic of the 21st-century.

The antiviral drugs Relenza and Tamiflu, which target the neuraminidase (NA) enzyme, successfully treated the infection but widespread use of these drugs has led to a series of mutations in NA that reduce the drugs' effectiveness.

Clinical studies indicate that the double mutant of swine flu NA known as IRHY2 reduced the effectiveness of Relenza by 21 times and Tamiflu by 12,374 times—that is, to the point where it has become an ineffective treatment.

To understand why the effectiveness of Relenza and Tamiflu is so seriously reduced by the occurrence of this mutation, the researchers performed long-timescale molecular dynamics (MD) simulations using GPUs.

Professor Mulholland said: "Our simulations showed that IRHY became resistant to Tamiflu due to the loss of key hydrogen bonds between the drug and residues in a part of the NA's structure known as the '150-loop'.

"This allowed NA to change from a closed to an open conformation. Tamiflu binds weakly with the open conformation due to poor electrostatic interactions between the drug and the active site, thus rendering the drug ineffective."

These findings suggest that drug resistance could be overcome by increasing hydrogen bond interactions between NA inhibitors and residues in the 150-loop, with the aim of maintaining the closed conformation.

Journal Reference:

New Effective Treatment for Tinnitus?
ScienceDaily (May 28, 2012) — A team of researchers from Maastricht, Leuven, Bristol and Cambridge demonstrated the effectiveness of a new tinnitus treatment approach in the journal The Lancet. Tinnitus is the perception of a noxious disabling internal sound without an external source. Roughly fifteen percent of the population suffers from this disorder in varying degrees along with the associated concentration problems, sleep disturbances, anxiety, depression and extreme fatigue.

Sometimes this disorder is so disruptive it seriously impairs their daily functioning and, unfortunately, there is no cure.

The research conducted by Rilana Cima and her colleagues, however, indicates that cognitive behavioural therapy can help improve the daily functioning of tinnitus patients.

The study, conducted at Adelante Audiology & Communication, followed 492 adult tinnitus patients for a period of twelve months. The effectiveness of an innovative tinnitus treatment protocol was compared to the standard treatment methods offered throughout the Netherlands. The ground-breaking, stepped treatment plan consists of cognitive behavioural therapy and combines elements from psychology and audiology. The therapy aims at reducing the negative thoughts and feelings surrounding tinnitus, symptoms through exposure techniques, movement and relaxation exercises, and mindfulness-based elements.

This is supplemented with elements from the so-called tinnitus retraining therapy (TRT), which examines the problems on a sound perception level. The treatment is offered by a multidisciplinary team of audiologists, psychologists, speech and movement therapists, physical therapists and social workers.
The project was funded by the Netherlands Organisation for Health Research and Development (ZonMW), and directed by Johan Vlaeyen, professor behavioural medicine at KU Leuven and Maastricht University.

The results offer compelling evidence to support the effectiveness of this innovative and specialised tinnitus therapy over more traditional forms of treatment. The overall health of the tinnitus patient improves and the severity of their symptoms and perceived impairment decreases after therapy. Moreover, the new treatment is far more effective in reducing negative mood, dysfunctional beliefs and tinnitus-related fear). The specialised tinnitus treatment is effective for both milder and more severe forms of the disorder. The researchers are therefore advocating a widespread implementation of this new treatment protocol.

**Journal Reference:**

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**Ukraine’s Sex Industry Bets on Euro 2012**
Agence France Presse, (05.29.2012)

Ukraine’s sex workers are counting on the country hosting the Euro 2012 soccer championship to bring in clients and cash. Concurrently, however, AIDS advocates are issuing stark reminders that the nation has the highest HIV infection rate in Eastern Europe.

Hundreds of thousands of fans are expected for the games, which begin June 8 in Warsaw, Poland, and end in Kiev, Ukraine’s capital. According to the International HIV/AIDS Alliance, Ukraine is home to between 52,000 and 83,000 sex workers—11,000 in Kiev alone. Other eastern Ukraine tournament venues in Donetsk and Kharkiv have some 3,000 sex workers, while Lviv is home to nearly 2,500.

UNAIDS reports upwards of 350,000 Ukrainians age 15 and over are HIV-positive. Further, a 2011 study by the International HIV/AIDS Alliance asserts that 24 percent of prostitutes in Kiev and 38 percent of those in Donetsk are HIV-positive.

One Ukrainian sex website claims Kiev prostitutes are even attempting to gain a competitive edge by studying the histories of participating nations, as well as the basics of soccer. Although Kiev prostitutes and brothels contacted by Agence France Presse said they realize the risks and use condoms, only 60 percent rule out unprotected sex. Others, as many as 22 percent according to 2010 survey data, are willing to forgo condom use for an added fee.

Fearing a rise in sex tourism related to Euro 2012, Ukrainian feminist group FEMEN is waging a campaign saying “Ukraine is not a brothel.”

European soccer’s governing body, UEFA, also has launched a campaign championing condom use.

“Show HIV and AIDS the red card. The HIV virus doesn’t play fair, so you have to,” says the campaign.

**IPS, AlertNet Report On Health Issues Resulting From Climate Change**

Inter Press Service examines the relationship between climate change and family planning in least-developed countries (LDCs), writing the "double challenge of mitigating climate change and combating crushing poverty makes improving reproductive rights and promoting gender equality imperative that can no longer be delayed, according to several recent reports and agreements." IPS highlights several reports and agreements, including an agreement between U.N. Women and the Organisation Internationale de la Francophonie (OIF) that "aims at tackling gender inequality in the 75 OIF member states, most of which are also LDCs"; an agreement between U.N. Women and the European Union "to strengthen cooperation between the two organizations in their work on gender equality"; and the Royal Society of London’s People and the Planet report, "which focuses on reproductive rights and social justice as cornerstones of global economic sustainability" (Godoy, 5/30).

In related news, AlertNet reports on an increase in malnutrition as a result of climate change in some countries in South Asia, writing, "Malnutrition is worsening in developing countries like Pakistan, Bangladesh, Nepal and India because of the impacts of climate change—particularly on water resources, a key input for producing food for more than a billion people in the region." The news service writes, "Climate change, growing use of food crops as a source of fuel and soaring food prices are three major challenges that threaten efforts to overcome food insecurity and malnutrition according to 'Impact of Climate Change and Bioenergy on Nutrition,' a joint report [.pdf] by the International Food Policy Research Institute (IFPRI) and the U.N. Food and Agriculture Organization" (Shaikh/Tunio, 5/29).
CIA's Use Of Health Workers In Intelligence Operations Could Hurt 'Innocent People'
"The CIA's vaccination gambit put at risk something very precious—the integrity of public health programs in Pakistan and around the globe" and has "also added to the dangers facing nongovernmental organizations (NGOs) in a world that's increasingly hostile to U.S. aid organizations," opinion writer David Ignatius writes in a Washington Post opinion piece. Noting that attention in the U.S. has focused on a 33-year prison sentence given to Shakil Afridi, a doctor convicted of treason for helping the CIA track down Osama bin Laden through a vaccination program, Ignatius says, "Afridi and his handlers should reckon with the moral consequences of what they did. Here's the painful truth: Some people may die because they don't get vaccinations, suspecting that immunization is part of a CIA plot."

Ignatius states that the number of polio cases is increasing in Pakistan, Afghanistan, and Nigeria, "in part because people believe conspiracy theories about vaccination," and notes that the WHO has warned that if the disease's spread cannot be stopped, "polio eradication will fail." He concludes, "Intelligence operations, by definition, operate in a gray area where the normal legal and ethical rules get fuzzy. But this case makes me wonder if some intelligence tactics, such as using health workers overseas, should be off-limits: If the operations are blown, the consequences will be too damaging, in unintended ways, to innocent people" (5/29).

Implications Of Eradicating Polio, Or Failing To Do So, Go Beyond Public Health
In this Atlantic opinion piece, Rachel Hills, a freelance writer based in London, examines the WHO's decision on May 25 to declare polio a public health emergency, "calling for the 194 member states to fully fund the Global Polio Eradication Initiative, and fill the currently $945 million gap in its budget for 2012-13." She writes, "Few people probably associate the phrase 'global health emergency' with polio, a disease that has been around for 5,000 years and is on a decades-long decline so steep that there are less than a thousand recorded cases left on Earth," but "polio's threat is still very real, and the mission to finally stamp it out forever is a crucial one for reasons even bigger than the disease itself."

She states that "polio is a different type of emergency than the ones we usually hear about in the news," writing, "Its biggest danger isn't the current number of cases, but the implications for failure: not only because a failure to eradicate could allow for a resurgence that could kill or disable thousands of children each year, but because of what it holds for the effectiveness of our global health systems itself." One implication "has to do with money," she writes, noting, "Over the past quarter century, $9.5 billion has already been spent on polio eradication, driven by international organizations." She writes that the other element "is symbolic," as "polio will be a marker of either what the world can or cannot achieve in global health." She concludes, "In public health circles, it is common to hear about the 'symbolic' importance of polio: how halting it would be a victory for public health, and how not taking advantage of the opportunity when the number of cases is so low would be a failure so devastating that it would make it difficult to pursue more such worldwide projects" (5/29).

Oceans Provide Healthy, Renewable Way To Meet Hunger Demand Of Growing Population
"With a growing population and an onslaught of new planetary pressures expected to limit terrestrial food production, the conversation about how we're going to feed a hungry planet should include the oceans," Andrew Sharpless, CEO of Oceana, and actor Ted Danson write in the Huffington Post's Green blog.
"We need to produce 70 percent more food to meet the coming hunger needs, with meat production alone increasing from 270 million metric tons in 2009 to 470 million metric tons in 2050, according to the U.N. Food and Agriculture Organization," they continue, adding, "The oceans will provide us an opportunity to meet that demand in a way that's eternally renewable, but only if we start taking the appropriate steps right now."

"Restoring the health of the oceans through a few basic principles in targeted areas around the world will benefit marine ecosystems and allow us to responsibly feed 700 million people every day, up from 450 million people at current levels," they write, noting, "The places we need to focus on are fortunately located in waters controlled by just a few nations, which means policies implemented on a country-by-country basis can help protect the majority of the world's marine fish." They conclude, "What we have here is an opportunity to make a tangible difference in the battle against global hunger while restoring the health and bounty of the world's oceans. What a rare opportunity to benefit both man and ocean all at the same time" (5/29).
**When is it ethical to prescribe placebos?**

The American Medical Association's Code of Ethics prohibits physicians from prescribing treatments that they consider to be placebos unless the patients know this and agree to take them anyway. But this policy is not clearly the best way to protect or benefit patients, concludes an article in the Hastings Center Report. A commentary by two AMA bioethicists responding to the article also appears in the journal.

Placebos are commonly understood to be inert treatments, such as sugar pills, that have no pharmacological effect, but the AMA defines placebos more narrowly, as therapies that a physician believes lack a specific pharmacological effect on the conditions being treated. The physician's belief may or may not align with the prevailing medical view of a treatment. "There are borderline and controversial cases, such as acupuncture and antidepressants, in which individual physicians might reasonably disagree with the medical community's consensus about whether a treatment is an active treatment or a placebo," writes Anne Barnhill, a philosopher and bioethicist who is studying social work at Columbia University.

The article cites a recent poll of American internists and rheumatologists that found that a significant number of them admit to giving patients placebos without disclosing the therapies as such. While some placebo use is patently unethical – providing a treatment that "has no scientific basis and is dangerous, is calculated to deceive the patient by giving false hope, or which may cause the patient to delay in seeking proper care" – other uses of placebos are widely seen as ethical, writes Barnhill.

Some placebos might offer medical benefit to patients with certain conditions, Barnhill notes, and the limited available data suggest that placebos are more effective when presented as active treatments. As a result, she adds, some bioethicists have argued that an undisclosed placebo is the best available treatment for some patients. "If the best available treatment is sometimes an undisclosed placebo," she writes, "then the AMA's policy prohibits physicians from offering the best available treatment in some cases."

In addition to failing to benefit patients, the AMA policy may not meet two of its other goals: protecting patients' autonomy and their trust in physicians. The rationale for requiring physicians to disclose their belief that a treatment is a placebo is that patients need this information in order to give informed consent about whether to take the treatment. Informed consent is essential to patient autonomy. But it is unknown whether patients find this information relevant to their decision-making, Barnhill says, because "there's little data on patients' attitudes toward placebos."

Because of this lack of data, Barnhill also argues that the AMA policy does not help protect patients' trust in physicians. "The AMA seems to assume that uncovering undisclosed placebo use reduces patients' trust in physicians. But this is not a given," she writes. "When they uncover undisclosed placebo use, patients might conclude that their physicians are untrustworthy liars or quacks, or that their physicians do not believe that they are truly sick – or, that their physicians are open-minded, cutting-edge, and savvy about mind-body connections."

Barnhill recommends that the AMA consider revising its policy on placebo use. If the goal is to protect patients from harm, safeguard their trust, and respect their autonomy, she says, then rather than requiring physicians to disclose their personal belief about whether a treatment is a placebo, the policy might require physicians to report on the medical community's consensus on the treatment's status.

In the same issue of the Hastings Center Report is a commentary by Bette-Jane Crigger, director of Ethics Policy for the AMA and secretary of the Council on Ethical and Judicial Affairs, which wrote its ethical guidelines on placebo use, and Matthew K. Wynia, director of the AMA's Institute of Ethics. Regarding Barnhill's recommendation that the placebo policy be based on professional consensus, rather than individual doctor's judgment, they write, "We'd be tempted to agree but, as in so much of medicine, it isn't clear that a strong consensus is actually possible here." How, they ask, should doctors distinguish between so-called impure placebos – medications that have a pharmacological effect on some illnesses but not necessarily for the ones for which they are being prescribed – from off-label prescribing?

Crigger and Wynia emphasize that the overarching intent of AMA policy is to encourage physicians to be honest with their patients. "If there is professional disagreement on how or whether a particular pharmacologic agent works, then patients deserve to know that," they write. "If a doctor holds an outlier view, then his or her patients deserve to know that as well.
Potential New HIV Vaccine/Therapy Target

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ScienceDaily (May 30, 2012) — After being infected with simian immunodeficiency virus (SIV) in a laboratory study, rhesus macaques that had more of a certain type of immune cell in their gut than others had much lower levels of the virus in their blood, and for six months after infection were better able to control the virus.

SIV is a retrovirus that infects primates. Strains of SIV that crossed over to humans resulted in the evolution of HIV. In rhesus macaques, SIV causes simian AIDS (though in many primates it is harmless) and studying the virus in these animals offers crucial insights into how HIV acts in humans, the researchers said.

The discovery by researchers at UCSF may shed light on the mystery of why some people infected with HIV are better able to control the virus, live longer and have fewer associated health problems than others who have been infected as long, they said. It also provides a potential new target for developing therapies or vaccines.

The cells that have the protective effect, called Th17 (T helper 17) cells, are a subset of the type of disease-fighting immune cell targeted and killed by HIV and found in the gut of both primates and humans.

A prior study from the same UCSF team found that SIV infection causes a normally protective immune response to infection to go awry, leading to reduction in the protective activity in the gut of these Th17 cells and weakening of mucosal defenses against bacteria. Interestingly, in that study, Th17 cells were not affected by SIV in another primate, African green monkeys, in which SIV infection is harmless and does not cause disease.

"Animals with more of these Th17 cells were better able to control SIV and this was due in part to macaques developing a more effective immune response by producing more SIV-specific CD4-positive T-cells to fight the infection. Our next step is to see if we can augment the Th17 effect, perhaps by looking at interleukin 17 (IL-17), the cytokine released by these cells, and testing to see if it has an effect," said the study's primary investigator, Dennis Hartigan-O'Connor, MD, PhD, assistant professor of medicine at the UCSF Division of Experimental Medicine.

"Further, if a treatment can be developed to increase Th17 cells in the gut, it may allow for a more effective immune response after exposure to an HIV vaccine or the virus itself," he added.

The findings are being published in the May 30, 2012 issue of Science Translational Medicine.

In the new study, the investigators first determined the levels of Th17 cells in the gut of sixteen rhesus macaques and then infected them with SIV. They found that the animals with more Th17 cells to begin with were better able to control the virus. They then gave animals drugs that deplete Th17 cells and found that reducing the number of Th17 cells made controlling SIV more difficult for those animals.

"We found great variation in the levels of Th17 cells, with as much as a five-fold difference in numbers between animals. e are not sure why this is the case. It could be genetically determined or perhaps due to a previous exposure to a type of bacteria that stimulates production of Th17 cells," said Hartigan-O'Connor.

This study is part of a series of investigations undertaken by researchers at the UCSF Division of Experimental Medicine into how SIV, and by extension HIV, interacts with the immune system in the gut. The previous study was focused on chronic infection and persistent inflammation in the gut.

"The earlier study addressed the cause and consequence of inflammation after infection. We found that inflammation induces an enzyme that knocks out Th17 cells, which normally help to keep the gut intact, and that disease progression was faster. Reciprocally, we have now found that animals do better if they have many Th17 cells at the outset of infection. We are gradually increasing our understanding of this important aspect of the immune system and we are working to translate this understanding into an approach that benefits patients," said study senior author, Joseph M. McCune, MD, PhD, chief of the UCSF Division of Experimental Medicine.

**Journal Reference:**