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Depression has a significant impact on adherence to antiretroviral therapy, according to a meta-analysis published in the online edition of the *Journal of Acquired Immune Deficiency Syndromes*. The results of 95 studies involving 36,000 patients were examined by investigators, who comment “depression is consistently associated with nonadherence to HIV treatment.”

Depression was associated with poorer adherence in cross-sectional and longitudinal studies, in both resource-rich and resource-poor settings, and in all populations affected by HIV. “Interventions that target depressive symptoms and optimal utilisation of HAART [highly active antiretroviral therapy] may have maximal effects on health outcomes,” write the authors.

HIV therapy works best if all or nearly all of the recommended doses are taken correctly. However, many patients have difficulty adhering to their therapy, and poorer adherence has been associated with an increased risk of treatment failure.

Missing occasional doses of medication is usually due to simple forgetfulness and is unlikely to have any clinical significance. However, poorer adherence can be related to social circumstances or co-morbid conditions, including mental health problems.

Depression and depressive symptoms are common in patients with HIV, with some studies finding a prevalence of 36%.

Many studies have looked at the relationship between depression and poor adherence to HIV therapy, but until now there has been no meta-analysis of their results, evaluating the strength and consistency of their findings.

Therefore a team of investigators lead by Dr Jeffrey Gonzalez of the Albert Einstein College of Medicine, New York, conducted a literature search to identify studies published since 1996 that examined the impact of depression or depressive symptoms on adherence.

A total of 95 studies involving over 36,000 patients met their inclusion criteria. Overall, the studies showed a highly significant relationship between depression and non-adherence (p < 0.0001).

The overall effect of depression on adherence was relatively modest (0.19). However, the investigators note that it was of a similar magnitude to that observed in a separate meta-analysis into the effect of depression on adherence in other chronic illnesses.

Studies that measured adherence by interview found a significantly stronger relationship between depression and non-adherence that studies employing self-completed questionnaires (p = 0.03).

Depression was equally likely to affect adherence in cross-sectional and longitudinal studies. Even mild symptoms of depression were associated with poorer adherence, the investigators commenting, “Our findings also suggest that the relationship between depression and HAART nonadherence is not limited to comparisons between those who meet the criteria for clinical depression and those who do not...studies that focused on depression diagnosis found equivalent effects to studies that measured depression as a degree of symptom severity.”

However, the meta-analysis was not able to show how depression affects adherence. The researchers speculate that it could be related to its impact on concentration, appetite, self-worth, or self-care.
They conclude, “novel approaches to the successful management of these linked problems could have significant public health benefits for patients living with HIV/AIDS.”

**Reference**

**House of Lords says UK needs new national HIV prevention campaign, bigger push for testing**

Keith Alcorn
Published: 01 September 2011
The United Kingdom government must give much greater priority to HIV prevention, and consider a new national campaign to inform the general public of the risks of HIV infection, according to a report issued today by the House of Lords Select Committee on HIV & AIDS in the UK.

Its report warns of “potentially huge cost implications…of failing to deal effectively with the epidemic,” and stresses that “the Government should ensure that HIV and AIDS is a key public health priority.”

Lord Fowler said that while up to £750 million a year is being spent on treatment, the Government is spending less than £3 million a year on prevention campaigns.

“I know these are difficult times, but if you were to try to find one good investment, it would be to spend more on prevention, because that investment prevents the treatment costs.”

The Select Committee was established in December 2010 in order to review the status of HIV responses in the United Kingdom and make proposals for improvements. Its recommendations are not binding on the Government, but do reflect the fruits of extensive hearings and submissions by more than 80 organisations which gave evidence.

The committee was chaired by Lord Fowler, who as Health Secretary in 1986 launched the `Don't Die of Ignorance‖ government information campaign on AIDS.

**Prevention and testing must expand**

Unsurprisingly, the committee has recommended a new national HIV campaign, or at the very least, integration of HIV prevention messages into all future sexual health campaigns.

Existing prevention activities targeted towards gay men and Africans need to be better funded, but a wider range of evidence-based approaches need to be adopted, and the effectiveness of these activities should be evaluated independently.

But it is HIV testing that the committee sees as the priority if HIV prevention efforts are to be improved.

“In particular, we want to see a new emphasis on people getting tested,” said Lord Fowler. “It is ridiculous that we have about a quarter of people with HIV who don’t know they have it. It’s bad for them, and it’s bad for public health.”

Testing needs to be offered outside sexual health clinics, and people need to be encouraged to test for HIV.

Opt-out HIV testing should be routinely offered to all patients registering with a new general practitioner, and to all patients admitted to hospital, in areas with a high background HIV prevalence. It should also be offered to all patients diagnosed with TB, and all clinicians should be better trained to recognise potential symptoms of HIV infection and AIDS, the committee says.

The committee also wants to see an end to the ban on home testing for HIV, subject to the development of careful regulations that will outlaw poor-quality testing kits and ensure that users can be linked into sexual health services.

The report criticises the current government approach to sex and relationships education in schools, which allows schools and parents to opt out. Schools should be legally obliged to provide sex and relationships education, this should include information on HIV, and teachers should be better trained to provide it, the committee recommends.

Another reason for a national campaign on HIV is to address prejudice and ignorance about the infection, the committee says. Work with faith leaders will be essential to reach African communities, and the development of people living with HIV as advocates will also play an important role in breaking down stigma.
Treatment

Treatment services should build stronger links with GPs, so that some elements of HIV care can be taken over by GPs, and clinics need to move towards offering evening and weekend clinics, home delivery of drugs, and email and telephone consultations, in order to reduce the burden on specialist services.

Procurement of antiretroviral drugs should be conducted on a national basis, the committee recommends, in order to achieve the greatest possible economies of scale, and to ensure that regions of the country outside current bulk purchasing agreements are not being over-charged. However the committee also notes that the priority in purchasing must be provision of drugs that are well tolerated and easy for patients to take.

People not currently entitled to free HIV treatment in the UK should receive free treatment.

Testing and treatment in prisons also needs to be improved, including national standards for treatment services within prisons.

The committee also recommends that priority should be given into research to evaluate the impact of treatment on new infections in the UK. It also recommends that research into the use of pre-exposure prophylaxis with antiretroviral drugs to prevent infection in HIV-negative people should be a funding priority for the National Institute for Health Research and the Medical Research Council.

Deborah Jack, Chief Executive of the National AIDS Trust, welcomed the recommendations.

"It is essential that HIV prevention is treated as public healthy priority by the Government and is a core element of new local public health strategies.

"The report covers more than 50 recommendations for action and it's important for the Government to act on these – not in a piecemeal fashion – but with a cohesive strategy for HIV which brings all these elements together."

Porn industry blasts condom campaign

September 1, 2011

A porn industry trade group blasted the AIDS Healthcare Foundation's campaign for mandatory condom use in the adult film industry and accused the organization of "grandstanding" and spreading misinformation.

The strongly worded statement issued Wednesday by the Canoga Park-based Free Speech Coalition came in response to complaints filed by the AIDS Healthcare Foundation with federal and Florida state health officials after the disclosure that an adult film performer tested HIV-positive.

The complaints call upon the Florida Department of Health and the Occupational Health and Safety Administration to investigate the incident and "take all appropriate steps to ensure that workers in the adult film industry are protected from the threat of sexually transmitted infections."

Diane Duke, director of the adult film industry trade group, said they have been falsely accused of withholding information about the incident from public health officials. She said there is no "authorized information" confirming a positive HIV test result and no county public health investigation underway.

As a precaution, Duke said the group is investigating and has called for a moratorium on production.

"AHF's campaign for mandatory condoms has done nothing but create controversy and, with the closure of AIM [clinic], has deprived the adult industry of an important health and safety resource," Duke said.

The AIDS Healthcare Foundation is trying to get a measure placed on Los Angeles' June 2012 ballot that would require adult film performers to use condoms in porn productions that seek city film permits. It would be the first time that voters are asked to weigh in on the issue.

In California, adult film performers must be tested every 30 days and show proof of a negative test before they perform, according to voluntary industry standards.

"Testing is not a substitute for condoms," said Michael Weinstein, president of the AIDS Healthcare Foundation. "Testing is not a form of prevention."

Using High-Speed Lasers To Zap Mosquitoes In The Fight Against Malaria

In this post on CNN's Global Public Square, journalist Amar Bakshi interviews Nathan Myhrvold, former chief technology officer of Microsoft and co-founder of Intellectual Ventures, about an anti-malaria project "that use[s] lasers and digital image processing techniques to not only find mosquitoes ... but also to determine the gender of the mosquito" before zapping female mosquitoes, which are responsible for transmitting malaria, out of the sky. Myhrvold told Bakshi, "Basically what we do is we look for the bug using a digital imaging processing. Then we shine the laser on it and measure the wing beat frequency and
the size and a couple of other parameters. And then we decide if this guy is a mosquito and if it is a female,” according to the blog (Todd, 8/21).

**UT MD Anderson scientists discover secret life of chromatin**

**DNA/histone combination, a destination for cell signals, also talks to other proteins**

HOUSTON—Chromatin—the intertwined histone proteins and DNA that make up chromosomes—constantly receives messages that pour in from a cell’s intricate signaling networks: Turn that gene on. Stifle that one.

But chromatin also talks back, scientists at The University of Texas MD Anderson Cancer Center report today in the journal *Cell*, issuing orders affecting a protein that has nothing to do with chromatin's central role in gene transcription—the first step in protein formation.

"Our findings indicate chromatin might have another life as a direct signaling molecule, that it can signal back to other proteins irrespective of gene transcription," senior author Sharon Dent, Ph.D., professor and chair of MD Anderson's Department of Molecular Carcinogenesis and director of the Center for Cancer Epigenetics.

In a series of yeast experiments, Dent and colleagues show that a signal through a histone protein regulates another protein called Dam1 that is involved in the separation of chromosomes during cell division.

**Signaling cascades don't dead-end at DNA**

"It's a basic change in our way of thinking about cell signaling — that all signals go into the nucleus and dead-end at DNA, that they point to chromatin and stop," Dent said. "Our data show that's not the case. We have a new fundamental aspect of cellular regulation that we need to now explore." DNA is tightly intertwined with histones and assembled in histone/DNA units called nucleosomes along the connecting length of a string of DNA. This structure is often described as being like beads on a string.

Genes are turned on by transcription factors, proteins that attach to the gene's promoter region and order the gene to make an RNA copy of its DNA that can be translated into a protein. Histone proteins regulate access to genes, blocking or facilitating transcription.

Histones and other proteins are modified by the attachment of chemical groups to specific spots on the protein. Attachment of a methyl group (a carbon atom joined to three hydrogen atoms) to a histone can help or hinder gene transcription depending on where the methylation occurs on the histone, Dent said.

**Crucial cross-talk between proteins**

In a 2005 Cell paper, Dent and colleagues reported that a methyl group-transferring protein called Set1 methylates the protein Dam1, which is part of a structure that assists in the orderly separation of chromosomes during cell division.

Set1 is part of a protein complex that works along with multiple regulatory factors to facilitate transcription by attaching methyl groups to a specific histone, H3, which was the only previously known target of Set1.

Dent's team set out to discover the exact mechanism by which Set1 methylates Dam1. To their surprise, they found that Dam1 methylation does not depend on gene transcription, revealing news roles for proteins formerly thought to be involved only in that process.

Rather, the crucial step is the attachment of a single signaling molecule called ubiquitin to a histone protein called H2B. This event was known to direct addition of methyl groups to histone H3, but Dent’s work indicates it is also required for methylation of Dam1.

Communication between H2B and Dam1 is the first such instance of cross-talk between histone and non-histone proteins, the authors report. The signaling connection between a chromatin change and a non-DNA-templated process such as chromosome separation is also new.

Connections between histone ubiquitination and histone methylation also occur in human cells, and mutations in a protein highly related to Set1, called MLL, are involved in leukemia. Dent’s work raises the possibility that histones can signal to non-histone proteins in human cells and that mismanagement of these events caused by MLL mutations might contribute to leukemia development.

Dent’s group is looking for other proteins that might be affected by histone modifications in both yeast and human cells. And they are studying the details of Dam1 methylation and its function in chromosome separation.
Black Death Pathogen Extinct?
The Yersinia pestis strain extracted from the bones of Black Death victims may no longer exist.
By Tia Ghose | August 29, 2011

Using a technique for extracting ancient DNA, researchers have found that the form of Yersinia pestis that caused the Black Death in medieval Europe may be extinct, according to a new study publishing today (August 29) in PNAS. The new approach could help researchers understand why that pandemic was so deadly.

“It’s a really interesting piece of work and really nicely done,” said Anne Stone, a biological anthropologist at Arizona State University. “Understanding the evolution of the bacterium is important for potentially predicting what future outbreaks might be like and why some outbreaks are worse than others.”

Between 1347 and 1350 the Black Death spread like wildfire from ports in Turkey to Italy, France, and England, killing around 30 to 50 million people, or a third to a half of Europe’s population. Researchers believe the plague bacterium, Yersinia pestis, was carried in ships by rats from its reservoir in Central Asia. Since then, there have been a series of less catastrophic outbreaks, and worldwide about 2,000 people still die of plague every year, said study co-author Hendrik Poinar, an evolutionary geneticist at McMaster University in Canada.

For years, Poinar and his colleagues have tried to characterize the bacteria responsible for the Black Death by amplifying DNA from the bones found in mass burial sites using PCR. “It was a nightmare,” he said, because only about 0.0001 percent of the DNA found in these bones is from the plague bacteria, with the vast majority coming from other environmental sources such as soil and plants, as well as the human hosts. In addition, after hundreds of years, environmental wear and tear has chopped up the bacterial DNA into tiny fragments no more than 50 base pairs long, Poinar added.

In the current study, the team used a strategy for extracting the DNA that had previously been used to extract mitochondrial DNA from Neanderthals. They used short sequences of DNA complementary to a portion of the modern Yersinia pestis genome to bind fragments in bone and teeth samples taken from plague victims buried in London. When they washed away all the extraneous DNA, they were left with short snippets of the bacterial DNA, which they then pieced together to recreate a plasmid of the plague-causing Yersinia pestis.

Comparing the plasmid to modern bacterial genomes, the researchers could find no exact match: the plasmid seemed to come from a strain that no longer exists. Modern plague victims are likely infected with different strains. In addition, the plasmid normally carries genes which affect how virulent the plague bacterium is, but the new sequence didn’t reveal any genes that would explain why the Black Death was so lethal, Stone said.

“It may be that other parts of the genome were important for making the pandemic particularly virulent,” she said. “But it is also a time when health care was basically nil,” so grim living conditions and sub-par medical treatment, rather than a particularly nasty strain of the disease, could have caused the higher mortality rate, she said.

The new method for extracting DNA could one day help answer why the Black Death was so deadly, Poinar said. “The million dollar question is, Can you use it to access whole genomes? Only when you have the entire genome will you be able to address that question,” he said.


Sharing the Bounty (long)
Gut bacteria may be the missing piece that explains the connection between diet and cancer risk.
By Michelle G. Rooks and Wendy S. Garrett | August 1, 2011

Like many great political alliances, symbiotic relationships in biology may have started with antagonism, before the two parties reached mutual understanding—at least according to some evolutionary biologists.
The often cited example is the mitochondrion, the eukaryotic cell’s energy-supplying organelle, which may have first existed as a prokaryote. As the story goes, this prokaryote was engulfed by a second cell, and the two eventually formed such a close symbiotic alliance that one could not live without the other. This mutual dependence, however, evolved over many millennia.

Our own symbionts, the microbes that reside throughout our bodies, primarily in our guts, have a more independent—some might say downright rocky—relationship with us, their hosts.

Although gut bacteria have long been called commensal (in which only one party derives benefit, but neither is harmed), it is now clear that we draw many benefits from their colonization of our body, some of which are essential to our health. Our relationship with gut bacteria is complicated, however. While involved in metabolizing food into energy, producing micronutrients, and shaping our immune systems, gut microbes are also increasingly being linked to medical conditions including obesity, inflammatory bowel disease, and diabetes. And our understanding of their influence continues to widen: these bacteria may play a critical role in cancer, either protecting us from it, or in some cases, promoting its initiation and progression.

**Bacteria, inflammation, and cancer**

One example of a dangerous gut microbe is *Helicobacter pylori*—a bacterium that resides in the GI tract of almost two-thirds of the world’s population, and is responsible for stomach ulcers in many people. Gastric MALT (mucosa-associated lymphoid tissue) lymphoma, a cancer that occurs in the stomach, is frequently associated with *H. pylori*. Not surprisingly, then, the antibiotics that kill this bacterium cause this particular cancer to regress in upwards of 80 percent of these patients, and half are cured. However, this infection is also an important risk factor for gastric cancer, which is much more difficult to treat, as antibiotics provide no cure. But harboring this bacterium does not automatically lead to cancer: the guts of some 4.5 billion people are home to *H. pylori*, yet stomach cancer occurs in only a fraction of individuals.

Gut microbes are increasingly being linked to medical conditions including obesity, inflammatory bowel disease, diabetes, and cancer.

Another example is a toxin-producing *Bacteroides fragilis* strain, which has been shown to initiate colon cancer in mice and may also do so in humans.¹ This bacterium’s toxin is a metalloprotease that can drive cleavage of the adhesion molecule E-cadherin, leading to the activation of the Wnt/β-catenin pathway, an overactive pathway in almost all colon cancers. The toxin also activates the transcription factor NF-κB, which plays an important role in the initiation and promotion of epithelial tumorigenesis and is best known as a master regulator of inflammatory response pathways. In this and other ways, this bacterial strain drives inflammation, which creates conditions that promote cancer formation and progression. Much of the current thinking about how bacteria may contribute to cancers, particularly those of the gastrointestinal tract, involves chronic inflammation. (See "An Aspirin for your Cancer?" *The Scientist*, April 2011.)

While many species of bacteria activate inflammation, it is when bacteria initiate chronic inflammation that cancer risk increases significantly. Inflammatory mediators, such as reactive oxygen and nitrogen species, are part of our defenses against bacterial pathogens, but persistent exposure to these mediators directly damages host DNA and contributes to genomic instability—a common feature of cancer cells. Certain cytokines and chemokines produced by immune cells function as growth factors or promoters of angiogenesis. NF-κB and STATs (signal transducers and activators of transcription), STAT3 in particular, are transcription factors vital to physiologic inflammatory responses, and are key molecular links connecting inflammation to cancer.²

The innate immune system’s microbial sensors, which recognize patterns shared across many microbes, have recently been shown to intersect with tumor growth pathways. Several studies in mouse models suggest that Toll-like receptors (a major family of receptors that bind these microbe-associated patterns) and their adaptor proteins, such as MyD88, can promote tumorigenesis by affecting both tumor size and number.

Additionally, the laboratory of Maria Abreu at University of Miami Miller School of Medicine, found that mice deficient in Toll-like receptor-4 were protected from colon cancers that usually arise in the setting of chronic inflammation.³ Conversely, when overexpressed, this receptor was associated with an increased susceptibility to colon cancer. Patients with colitis-associated cancer also had elevated Toll-like receptor-4 levels, raising the possibility of a novel therapeutic target.

To truly understand how gut bacteria might contribute to the initiation of diseases such as cancer, it is vital to clarify, at the molecular level, the beneficial role these microbes play in digestion and metabolism, and the ways that changes in the human diet affect the microbial residents in the gut.
Eating for two
Successful adaptation to the ever-changing human diet is central to the survival of gut microbes. The laboratory of Jeffrey Gordon at Washington University in St. Louis is answering key questions about how diet influences gut bacteria and what has made certain bacteria such successful symbionts. Several other laboratories, such as Andy Goodman’s at Yale, Ruth Ley’s at Cornell, Justin Sonnenburg’s at Stanford, and Peter Turnbaugh’s at Harvard, are now actively investigating the genetic features that allow these bacterial species to rapidly respond to dietary changes. The ‘Western diet,’ a dietary pattern high in fats and simple sugars, can reshape gut microbial ecology and predispose both mice and humans to obesity—a risk factor for cancers of the colon, endometrium (lining of the uterus), breast, esophagus, and kidney. Changing to a plant polysaccharide–rich, low-fat diet reduces weight and shrinks fat stores in humans and mice, and causes marked shifts in gut microbiota. Researchers observed that after these dietary changes had been adopted for long enough to reduce the weight of human subjects and mice, the gut microbiota profiles looked more similar to those of lean control subjects.

In a normal gut of a lean individual, bacteria generally do more good than harm. Gut bacteria actively supplement our metabolism. The indigestible leftovers of our diet serve as the major food source for these resident bacteria, the greatest numbers of which reside in the distal gut, or large intestine. They metabolize many dietary fibers that escape host digestion, generating short-chain fatty acids such as acetic, propionic, and butyric acids, which contribute an estimated 10 percent of our daily energy supply. The amount and variety produced are determined by the types of food ingested, how long the food stays in the gut, and which microbial species are present. While humans have the capacity to synthesize some short-chain fatty acids, the vast majority are produced by gut microbes.

These metabolites do more than just provide us with extra energy. Approximately 95 percent of gut short-chain fatty acids are absorbed and metabolized by the host for a wide range of physiological functions. Microbe-generated acetate, for example, has been shown to bind a G-protein-coupled receptor, GPR43, expressed on immune cells. Deletion of this receptor in mice exacerbated arthritis, asthma, and colitis—diseases characterized by an overactive immune system—suggesting that the microbially produced acetate may help guide the resolution of inflammatory responses. Acetate also appears to protect the host against infection by pathogenic bacteria, like the intestinal hemorrhage-causing Escherichia coli 0157:H7, by strengthening epithelial barrier function.

While acetate’s connection to health benefits is clearest, propionic and butyric acids may also be beneficial. Propionic acid appears to modulate T-helper cell immune responses by promoting the adaptive immune response. Butyrate’s role as an important energy source for certain epithelial cell types is well
established, as is its inhibition of histone deacetylase enzymes. Some of butyrate’s anticancer effects may involve its ability to alter microRNA expression. A recent study from the laboratory of Eugene Chang at the University of Chicago suggests that butyrate slowed the proliferation of a cancer cell line by reducing miR106b levels. This family of microRNAs plays important roles in regulating cell cycle progression and is often overexpressed in cancers.

**From food to cancer**
Researchers are beginning to realize that we can’t think of the food we ingest without thinking of the gut bacteria that also ingest our food. One oft-cited example is the polyphenol family of chemicals, predominantly found in coffee, tea, wine, fruits, and vegetables, which have been linked to reducing the risk of cancer. The three main classes of dietary polyphenols include flavonoids, phenolic acids, and lignans. Polyphenols are not digested and absorbed in the upper gastrointestinal tract, but they are readily metabolized in the colon by microbial enzymes.

While several members of the *Bacteroides* genus have been shown to metabolize polyphenols, determining which members of the colonic microbial community play a role in the metabolism of polyphenols will require both metabolomic and metagenomic approaches, as well as carefully crafted animal studies and human trials. Investigations headed by Tom van de Wiele’s group in the Laboratory of Microbial Ecology and Technology at Ghent University have shown that the type and quantity of polyphenols consumed by healthy human subjects results in distinct metabolic profiles that are unique to each individual and his or her microbiota. The metabolism of polyphenols changes how they will be absorbed and utilized; therefore, the variability of health benefits observed in epidemiological studies may be attributable to the composition and relative abundance of the gut microbiota. In addition, food isn’t our only source of polyphenols: clinical studies have shown that when human subjects are given a measured quantity of polyphenols, the amount of polyphenols excreted can exceed what was consumed.8

A number of polyphenols, produced by microbes or ingested directly, are being actively investigated for their anticancer properties. Ellagic acid, which is found in berries and nuts, is one of many plant polyphenol compounds thought to have anti-inflammatory and anticancer effects. Gut microbiota are essential for metabolizing ellagic acid into urolithins—compounds believed to be responsible for reducing inflammation and thereby protecting against cancer. The laboratory of Juan Carlos Espín de Gea at the Spanish National Research Council has investigated the anti-inflammatory effects of urolithins in chocolate. In cell culture, urolithin-A was found to downregulate mRNA expression and protein levels of cyclooxygenase-2—a prostaglandin synthase and a key inflammatory mediator that is inhibited by aspirin and other nonsteroidal anti-inflammatory drugs. They also showed that urolithin-A inhibited the
activation of transcription factors like NF-κB and signaling pathways that drive inflammation.\textsuperscript{2} Investigators from this lab have also observed similar results in vivo using a rodent model of intestinal inflammation.

Although it is known that a substantial portion of polyphenol metabolites are generated by bacteria in the gut, just how microbiota interact with polyphenols is still not fully understood. In some cases, polyphenols are toxic to microbes. Numerous flavonoid compounds have been able to kill both Gram-positive and Gram-negative organisms in vitro.\textsuperscript{23} In addition, it is not known how dietary phenols may alter microbial composition.

In other cases, polyphenols such as the isoflavones produced by soy and other plants act as antioxidants that mitigate oxidative stress, which is often linked to cancer. Just how soy may modify cancer risk is far from clear. Like other antioxidants, isoflavones are thought to reduce the inflammation that predisposes tissues to cancer. The soy isoflavone daidzein is metabolized by certain gut microbes into equol, a plant estrogen. Because of their hormone-like properties, soy isoflavones have been reported to have protective effects against prostate cancer; however, these findings are not consistent across studies. One reason for these inconsistencies could be individual differences in how gut microbes metabolize isoflavones. According to epidemiological studies, only 30–50 percent of the human population is capable of producing equol. Studies of populations that consume a high level of soy, mostly of Asian descent, have found that equol producers may have a greater reduction in cancer risk than those who do not produce equol.\textsuperscript{24} Generally, interpretation of the soy—cancer prevention literature is challenging. Although more research is needed to understand the role of our gut microbiota in mediating cancer risk, metabolites like urothilins, polyphenols and equol, show promise against cancer.

Our group is studying the effects of dietary interventions that are thought to be beneficial—such as fermented dairy products—and of risk-associated foods like red meat on the microbiota and on colon cancer. We use mouse models of inflammatory bowel disease and colon cancer to understand how diet can impact these diseases. By using mice, we can control many genetic and environmental factors that complicate human studies of the microbiota and diet. In addition, we make use of germ-free mice, in which we can design the microbial communities from scratch by adding back select bacteria. Also, we can transplant human fecal samples into such mice and thus, to some extent, make them better models of human physiology. Our research suggests that one way fermented milk products may confer a health benefit is by indirectly driving shifts in short chain fatty acids; bacteria in the fermented milk actually influence the resident gut microbes to drive these changes.

**An incomplete symbiosis**

Our gut microbiota, when fed certain foods, can also produce detrimental metabolites that promote cellular proliferation and inhibit apoptosis—circumstances conducive to cancer development. Heterocyclic amines (HCAs)—compounds found in the char that coats any well-done steak—are considered carcinogenic. HCAs are not digested in the small intestine but remain available for metabolism by bacteria in the colon. Once metabolized by gut bacteria, HCAs are converted to electrophilic derivatives that damage DNA, placing people at increased risk for colon cancer.\textsuperscript{10}

It will be years before a fecal sample will reveal risk of cancer or the foods that could change it.

Hydrogen sulfide is another metabolite produced by gut bacteria that can damage DNA. Consumption of high-protein foods, particularly red meat, may fuel hydrogen sulfide production by sulfate-reducing gut microbes. Some studies suggest that patients with colon cancer and inflammatory bowel disease may harbor higher levels of such bacteria. Studies by Rex Gaskins’s lab at the University of Illinois at Urbana-Champaign suggest that hydrogen sulfide can contribute to cancer progression when DNA repair mechanisms are impaired. Whether a greater abundance of sulfate-reducing bacteria precedes or is a result of these health conditions, and which host factors contribute, requires further investigation. In high-risk individuals, these metabolites may offer targets for cancer prevention.

**“It takes a village”: the power of community**

Although the link between gut microbes and cancer risk is becoming clearer, it will probably be years before dropping off a fecal sample at the doctor’s office will generate a report of your cancer risk and a list of foods you should or shouldn’t eat to modify that risk. Further experimentation is needed to understand the metabolic potential and function of the human microbiota. Some of the current bottlenecks are in data processing and analysis.

Indeed, because only a very few gastrointestinal-associated bacterial species, like *Helicobacter pylori*, have been convincingly linked to cancer, the focus is shifting from single-organism studies to bacterial communities as a factor influencing cancer risk. Worldwide consortia such as the Human Microbiome Project and the Metagenomics of the Human Intestinal Tract project (MetaHIT) are applying sequence-
based approaches to study the microbiota of healthy and disease-affected individuals. The emerging field of microbial "omics," which encompasses metagenomics and metabolomics, is rapidly advancing. Cancer genomics has offered the potential to understand how cancers operate at the molecular level.

Microbial metagenomics may have the potential to improve many aspects of cancer prevention and treatment. Current studies like the esophageal cancer microbiome project, a joint venture spearheaded by Karen Nelson from the J. Craig Venter Institute and New York University’s Zhiheng Pei, aim to identify microbiota-based biomarkers that can identify patients at high risk for developing cancer. Successful microbiota biomarker identification could be used as a prognostic, diagnostic, and management tool, allowing gut microbe testing to become part of the evolving personalized-medicine tool kit.

In cancer care, cancer genomics and pharmacogenomics are increasingly employed to identify which patients will respond to which treatments and whether particular patients are at risk for experiencing dangerous drug toxicities. Enzymes produced by gut microbes can often interact with drug regimens, contributing to side effects or changing how the drug is metabolized by the body. A recent study showed that gut bacterial enzymes called β-glucuronidases can contribute to the severe diarrhea sometimes associated with a commonly used colon-cancer chemotherapy drug called irinotecan. Selectively targeting these bacterial enzymes reduced a potentially life-threatening side effect of this drug.

The day may not be so far off when fecal samples are biobanked for future transplant, and microbiota associated with a high risk of cancer can be replaced with lower-risk microbiota. Foods or bacterial-directed therapies may be used to re-engineer the microbial communities in the gut by introducing functions that reduce cancer risk. As we come to understand what features constitute a healthy microbiota and how the microbiota changes across the human life cycle, the plasticity and genomic potential of our gut microbes may be tapped as a fountain of youth and the medical profession has yet to understand fully, what "normal" is.

Michelle Rooks and Wendy Garrett are at Harvard School of Public Health.

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References

Hilary Butler
statistics show that the bulk of the cancer explosion has come hard on the heels of the unbridled use of antibiotics as a sledgehammer for every cough and sniffle that abounds. Antibiotics are "anti" biotics, and when it comes to the metabolome, are a napalm bomb. Antibiotics should NOT be used routinely in animal-factory farming, and should only be used in humans as a last resort with attention paid to what else antibiotics napalm, other than the therapeutic target. Along with every antibiotic prescription, should come detailed information as to how to return the metabolome back to "normal". But there is a problem. The medical profession has yet to understand fully, what "normal" is.

eve barak
Fascinating. This is an unscientific scientific "territory" to me, but as a five-foot-two female who, just a couple of years ago, lost a pound a week for 80 weeks to drop from an obese 205 pounds to a healthy "size medium" 125 pounds (and has maintained it for the past couple of years) simply by changing my entire eating habits to a "healthy" Mediterranean-style (veggie-rich, blueberries-rich, yogurt-rich, olive-oil rich, whole-grain-rich, lots-of-fish but only occasionally red meat) regimen (with small-portion snacks of dry-roasted
edamame and peanuts and NO partially hydrogenated fats & practically NO sweets, cakes, candies, or other junk foods except at weddings and birthday parties), this is of great interest to me and, from a purely empirical perspective with no statistical significance (N=1), it makes sense.

**Christopher R lee**

Hydrogen sulfide is indeed toxic. It’s metabolised in gut wall cells to thiolsulfate, which doesn’t often get a mention. Thiolsulfate would be expected to protect these cells from potentially mutagenic electrophilic SN2-type compounds (including bacterial metabolites) that can react directly with DNA. I didn’t find anything on intracellular thiolsulfate concentrations but they could be high because it’s hard to see how this polar dianion gets out unless there’s a specific channel.

Thiosulfate has been used to protect non-target organs from anticancer alkylating agents, though it doesn’t get into the cells.

According to a recent paper (doi:10.1038/nature09415) the inflammatory pathogen Salmonella enterica serotype Typhimurium (S. Typhimurium) converts thiolsulfate to dithionite for use as a respiratory electron acceptor. If thiolsulfate is depleted during inflammation the cells might possibly be more vulnerable to electrophiles.

**Iwona Grad**

Very interesting overview. However, we already re-engineer the microbial communities by injecting for instance yoghurt containing life-bacteria or any other probiotic food supplement. There is a lot of data available on the benefits of such for immune system etc. The “healthy gut microbiota” is of crucial importance to body function not only through direct interaction with the host but also through keeping in check parasites and harmful microbes by pure territorial domination.

The ability of certain bacteria to affect the meningitis bacteria was evidenced years ago on fish in the fishyard. They had noticed ‘something’ seemed to be killing the meningitis bacteria and found the bacteria. I posited whether or not this could be accomplished in man to the point even the bacteria normally residing on the body would be helpful bacteria. I was castigated for my impudence. It seems since that is precisely where they are headed. The ‘garden within’ is the same as a garden in your back yard in which if you give it the proper fertilizer and plant the proper plants / bacteria you actually get a different ‘milieu’ within. As in the case of adding iron to all our food which leads to a certain bacteria.

"Many bacteria depend on iron for their growth; examples are Escherichia coli; Klebsiella, Pseudomonas, Salmonella, Yersinia, Listeria, and Staphylococcus species; and Haemophilus influenzae."

**dcedochbrain**

Very interesting overview! However, try to avoid perpetuating persistent mis-information regarding the SAD: "The 'Western diet,' a dietary pattern high in fats and simple sugars, can reshape gut microbial ecology and predispose both mice and humans to obesity."

While the high simple sugar (and processed carb) contain is certain, consider this: (from The Harvard School of Public Health).

The Nutrition Source, Fats and Cholesterol: Out with the Bad, In with the Good

In the 1960s, fats and oils supplied Americans with about 45 percent of their calories; (1) about 13 percent of us were obese and under 1 percent had type 2 diabetes, a serious weight-related condition. (2, 3) Today, Americans take in less fat, getting about 33 percent of their calories from fats and oils; (1) yet 34 percent of us are obese and 8 percent have diabetes, most with type 2 diabetes. (4, 5)

References:


**Lon Collapse**

It’s nice to see researchers recognizing the complexity of the body and its internal milieu. But what happens down the road when you try to get your healthy biome past the FDA in order to make the claims that your research has justified? Is there a reason that Align (R) consists of only one strain of bifidus infantis? What if the solution lies in many bacterial strains working together as you are suggesting? Will the FDA be satisfied with these complex solutions? When will we get to the understanding that the higher degree equations that more adequately represent the complexity of human physiology have a correspondingly higher number of solutions? Maybe we have even been integrated enough in our evolutionary heritage to be complex enough that the solutions are found in attractors. Let’s see how the FDA, mandated to show our drugs to be effective (which they do by forcing them into the linear logic of randomized double blind crossover trials), deals with attractors.

**Older anti-epileptic drugs associated with failure of HIV treatment**

**Michael Carter**

Published: 02 September 2011

An interaction means that some older anti-epileptic drugs and antiretroviral therapy should not be used together, a US study published in the open-access journal *AIDS Research and Therapy* shows.

Both types of therapy are metabolised by the body using the P450 pathway in the liver, reducing levels of anti-HIV drugs and leading to sub-optimal control of the virus.

Although the theoretical risk of a drug interaction is known from pharmacokinetic studies in healthy volunteers, this study provides strong clinical evidence that older anti-epileptic drugs should not be used in patients taking antiretroviral therapy.

Most of the anti-epileptics used in resource-limited settings use the P450 pathway, and the investigators believe the ramifications of the interaction with HIV therapy “may be substantial.”

HIV-positive individuals use anti-epileptic drugs widely. In addition to controlling seizures, they are also a therapy for neuropathy, depression and bipolar mood disorders.
Many first-generation anti-epileptic drugs such as phenytoin, carbamazepine and phenobarbital are metabolised by the P450 enzyme. The same pathway is also used by antiretroviral drugs in the protease inhibitor and non-nucleoside reverse transcriptase (NNRTI) classes as well as the CCR5 inhibitor maraviroc.

Because these medications are metabolised in a similar way there is a potential for interactions. These could lead to reduced blood levels of antiretroviral drugs and therefore inadequate control of HIV.

Investigators therefore retrospectively compared virologic outcomes in patients taking antiretroviral therapy with P450-inducing anti-epileptics with two control populations.

The first consisted of patients who were taking HIV treatment and anti-epileptics that did not use the P450 pathway; the second comprised patients who were only taking HIV therapy.

Virologic failure was defined as lack of viral suppression to below 400 copies/ml six months after the start of therapy, or a sustained rebound to above 400 copies/ml after a period of undetectable viral load.

A total of 19 patients were treated with concurrent HIV therapy and anti-epileptic drugs that used the P450 pathway.

These patients were significantly more likely than the 85 individuals taking anti-epileptics that did not use this pathway to experience virologic failure (63% vs. 27%; p = 0.009).

After both six and twelve months of therapy, patients taking the older anti-epilepsy drugs were less likely to have an undetectable viral load than the patients taking non-P450-inducing epilepsy therapy (33% vs. 71%, p = 0.016; 36% vs. 75%, p = 0.018).

The risk of treatment failure was increased four-fold for patients taking P450-using anti-epileptics compared to patients taking epilepsy drugs that did not use this pathway (OR = 4.19; 95% CI, 1.54-11.44, p = 0.005).

Rates of virologic failure were also higher among the patients taking older epilepsy therapy when compared to individuals not receiving anti-epileptics (63% vs. 43%). Differences in outcomes between these two groups were significant when the investigators took into account baseline viral load (p = 0.046).

“This study is the first demonstrating clinically meaningful outcomes in participants receiving overlapping treatment with [P450-inducing anti-epileptic drugs] and HAART,” comment the investigators.

They emphasise, “the impact is so robust, that we were able to demonstrate this despite the small numbers of patients receiving [P450-inducing anti-epileptic drugs].”

The researchers recommend that wherever possible HIV-positive patients should receive anti-epileptics that do not use the P450 pathway.

However, in many resource-limited settings the only available epilepsy drugs are older therapies with a risk of interactions.

In these circumstances the investigators recommend closer clinical monitoring, and if possible the use of HIV therapy that does not involve a risk of interactions.

They note that one antiretroviral option would be raltegravir. But they acknowledge that its price means that it is not readily available in poorer countries. Another possibly offered by the researchers is triple NRTI therapy, but the poor virological outcomes associated with such regimens are also noted.

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US Male Circumcision Rates at Hospitals Dip—CDC
Reuters, (09.01.2011)  Julie Steenhuysen
The proportion of newborn males being circumcised has slightly declined in the United States in the past decade, according to a new CDC analysis of three independent national databases. In the decade previous to that studied, rates of in-hospital circumcision had increased.

Incidence of newborn male circumcision declined from 62.5 percent in 1999 to 56.9 percent in 2008, according to CDC’s National Hospital Discharge Survey. NHDS uses an 8 percent sample of short-stay hospitals, or those with general medical or surgical specialties, from 50 states.

The rate declined from 63.5 percent in 1999 to 56.3 percent in 2008 in the Nationwide Inpatient Sample, which is based on a 20 percent sample of US community hospitals (non-federal, short-term, general and other specialties) from 42 states.

The rate also declined—from 58.4 percent in 2001 to 54.7 percent in 2010—in Charge Data Master, private firm SDIHealth’s convenience sample of health care reimbursement claims from a 20 percent sample of US short-stay, acute-care, and non-federal hospitals in 48 states and the District of Columbia.
In the preceding period, in-hospital newborn male circumcisions increased from 48.3 percent in 1988-1991 to 61.1 percent during 1997-2000.

The authors referenced “three recent studies showing that circumcision of adult, African heterosexual men reduces their risk of acquiring [HIV] and other sexually transmitted infections.” Circumcised males have reduced risk of herpes, human papillomavirus, and genital ulcer disease. Their female partners are at reduced risk of HPV infection, trichomoniasis, bacterial vaginosis, and genital ulcer disease.

Critics of infant male circumcision, including activists who recently failed in their attempts to let voters decide if the procedure should be banned in San Francisco, liken it to female genital mutilation.

The researchers did not explore the reasons behind the decline. However, they cited a study showing that circumcision rates were 24 percent higher in states whose Medicaid plan covers the procedure compared to those whose plan does not. Thirty-three states provided this coverage in 2009.

New insight in how cells’ powerhouse divides
September 2, 2011

New research from the University of California, Davis, and the University of Colorado at Boulder puts an unexpected twist on how mitochondria, the energy-generating structures within cells, divide. The work, which could have implications for a wide range of diseases and conditions, was published today (Sept. 2) in the journal Science.

professor and chair of molecular cell biology at UC Davis and a co-author of the paper.

Mitochondria produce chemical energy for a cell’s needs. They are wrapped in two membranes, have their own DNA, and can divide to produce new mitochondria. When this division is not properly controlled, it can result in cell death. Defects in mitochondria have been linked to a wide range of degenerative conditions and diseases, including diabetes, cardiovascular disease and stroke.

The research team led by Gia Voeltz, assistant professor in the Department of Molecular Cell and Developmental Biology at CU-Boulder, and Nunnari, at UC Davis, investigated how another structure in the cell, the endoplasmic reticulum or ER, is related to mitochondrial division.

The ER is a complex network of sacs and tubules that spreads out from the nucleus and is distributed throughout the cell. It is thought to play a role in a range of cell processes, including making secretory protein and lipids, and transporting molecules around the cell.

The team found that in both yeast and mammalian cells, mitochondrial division overwhelmingly occurred at points where the two structures, mitochondria and ER, touched.

Previous work by Nunnari’s lab and others has shown that mitochondrial division is regulated by dynamin related protein-1, which assembles into a ligature that tightens around the sausagelike mitochondrion and causes it to divide.

mitochondrial division were also found where the ER and mitochondria touched. Their study indicates that ER tubules first squeeze the mitochondrion, then dynamin-related proteins assemble on the surface to complete the job. This new function for the ER expands and transforms our view of cell organization, Nunnari said.

Persistent Immunity: Researchers Find Signals That Preserve Anti-Viral Antibodies
ScienceDaily (Sep. 2, 2011) — Our immune system is capable of a remarkable feat: the ability to remember infections for years, even decades, after they have first been encountered and defeated. While the antibodies we make last only about a month, we retain the means of making them for a lifetime. Until now, the exact mechanism behind this was poorly understood, but researchers at The Wistar Institute have discovered some of the protein signals responsible for keeping the memory of distant viral infections alive within our bodies.

Their study, presented in the Journal of Clinical Investigation, may aid scientists in creating better, more effective vaccines.

"We are particularly interested in how our bodies generate antibodies against viruses and how we maintain anti-viral antibody secreting cells as a hedge against future infection from the same virus," said Jan Erikson, Ph.D., senior author of the study, professor in Wistar’s Immunology Program and a member of The Wistar Institute Vaccine Center. "Our study highlights how protein signals sustain the cells that make antibodies against viruses in perpetuity, which we believe is crucial knowledge for the development of vaccines for lasting protection against the flu, for example."

Despite an annual vaccine against the disease, seasonal influenza remains a potent killer, one associated with nearly half a million deaths each year around the globe. The persistence of antibody
memory is why older people, who typically suffer more from influenza, fared much better than expected during the 2009 avian influenza pandemic. Previous exposure to—or vaccination against—a similar strain provided many older Americans a resistance to the 2009 avian flu. Wistar Vaccine Center researchers are among a number of teams of scientists working toward a universal flu vaccine, one that would forgo the need for an annual flu shot.

The main role of vaccines is to stimulate the production of antibodies that bind to portions of the infectious agent. Once bound, the antibodies provide a target for the immune system, allowing immune cells to attack it or any infected cells in order to clear away disease. Antibodies are highly variable proteins that are produced in huge quantities by a subset of white blood cells, called B cells, that have transformed into antibody factories, termed antibody secreting cells (ASCs). Our immune system produces a broad array of antibodies, but during an infection with a virus, for example, the immune system allows the predominant production of antibodies that are directed against the virus. The cells making these particular antibodies are then selected for preservation.

According to Erikson and her colleagues, this act of preservation requires signals, provided by proteins called BLyS and APRIL. Mice that have been exposed to influenza require these proteins in order to sustain anti-influenza ASCs in their lungs. The researchers found that neutralizing BLyS and APRIL reduced the numbers of anti-viral ASCs found in the lungs and bone marrow, yet interestingly, did not affect the ASCs found in spleen or in lymph nodes nearby the lungs.

BLyS and APRIL bind to another protein called TACI, a receptor found on the surface of ASCs, which the researchers see as an important translator for marking the ASCs that will become long-lived.

"We know from humans that the absence or mutation of the TACI gene leads to common variable immunodeficiency disease (CVID) and these patients suffer from recurrent respiratory illnesses because of low amounts of certain antibodies in their bronchial secretions," said Amaya I. Wolf, Ph.D., the study's lead author and a postdoctoral fellow in the Erikson laboratory. "Our studies show that mice that lack TACI can mount an initial B cell response to viral infection—and are able to produce antibodies to flu—but these mice fail to maintain anti-viral ASCs over a long period of time. Importantly, we show that this results in lower anti-viral antibody titers, and mice are less protected against a secondary viral attack at a later time."

"After resolution of a viral infection we want to have ASCs in our lungs to guard our mucosal surfaces, the port of microbial entry, in case of a reinfection with the same virus," Wolf said. "The lung microenvironment after a viral infection allows the ASCs to persist as a sort of local base, a place for the local release of protective antibodies."

"To avoid damage of the lung tissue, the immune system wisely evolved means of keeping the secretion of antibodies under tight control," Wolf explained. "The anti-viral ASCs in the lungs are short-lived and require BLyS and APRIL for their more immediate survival, but also the generation of longer-lived ASCs that take up residence in the bone marrow depends on these signals."

According to Wolf, it might be possible to manipulate ASC behavior to prolong or strengthen the effectiveness of vaccines. Drugs that induce targeted production of ASC survival factors, such as BLyS and APRIL or manipulation of their signals through TACI, their receptor, could theoretically help to maintain specific antibodies. While the seasonal flu is constantly mutating—necessitating an annual vaccine—even weakly reactive antibodies could be protective if there are enough of them and if their production is sustained.

One interesting observation from this study, the researchers say, is that the persistence of ASCs in different tissues appears to be regulated differently. This has spurred plans for the Erikson laboratory to conduct a genome-wide molecular survey in collaboration with Wistar Professor Louise Showe, Ph.D., director of Wistar's genomics facility.

**Journal Reference:**
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**Cryptococcus Infections Misdiagnosed in Many AIDS Patients, Study Suggests**

ScienceDaily (Sep. 1, 2011) — Most AIDS patients, when diagnosed with a fungal infection known simply as cryptococcosis, are assumed to have an infection with *Cryptococcus neoformans*, but a recent study from Duke University Medical Center suggests that a sibling species, *Cryptococcus gattii*, is a more common cause than was previously known.
The difference between these strains could make a difference in treatment, clinical course, and outcome, said Joseph Heitman, M.D., Ph.D., senior author of the study and chair of the Duke Department of Molecular Genetics and Microbiology.

The study was published Sept. 1 in *PLoS Pathogens*.

The study emphasizes that health professionals need more careful recording of the cryptococcal species to understand different clinical courses and possibly to change treatment strategies.

Researchers at Duke University Medical Center discovered that in the Los Angeles area, over 12 percent of AIDS patients diagnosed with *Cryptococcus* were infected with *C. gattii*, much higher than earlier studies, suggesting only about 1 percent have *C. gattii*. The researchers based these figures on molecular testing of fungal DNA barcodes.

This discovery comes at the same time as a *C. gattii* outbreak is expanding in the Pacific Northwest, spreading southward from Vancouver, British Columbia, through Washington, Oregon, and into northern California. Molecular testing is helping both health officials and scientists gain a picture of how a formerly tropical fungus could find new territory, in temperate climates, for infection.

"Importantly, we found that isolates causing the outbreak and those infecting AIDS patients are completely different (VGII vs. VGIII)," said co-lead author Edmond Byrnes, Ph.D., a recently graduated student in the Heitman laboratory.

Wenjun Li, Ph.D., also a co-lead author and researcher in the Heitman laboratory, noted that, based on the fungal isolate samples taken from patients, those with *C. gattii* may experience resistance to the commonly used "azole" drugs that combat fungal infections, and clinicians might be better aware of potential treatment problems if they knew the species.

Because cryptococcal strains are responsible for over 620,000 deaths annually and responsible for one-third of all AIDS deaths, this species distinction may be of public health importance.

"There may be an unrecognized health burden in AIDS patients attributable to *C. gattii* rather than *C. neoformans*," Heitman said.

He said that while a simple test is all that is needed to distinguish the two strains, "few clinical microbiology labs or hospitals, even in developed countries, are equipped to distinguish *C. neoformans* from *C. gattii*."

Heitman said that he doesn't believe that there is any human-to-human transmission of *C. gattii*, but rather, patients are being exposed in the environment. For example, one AIDS patient from San Diego had an isolate that was traced back to a type of tree, which is a common place to find *C. gattii*, in Australia and elsewhere.

"This study clearly illustrates that AIDS patients in certain areas of the world might be infected by two different cryptococcal species," said John R. Perfect, M.D., professor of medicine at Duke University Medical Center. "Although the outcome of infection in comparison between the two species remains uncertain, this study shows that we need to carefully control for potential differences and study them further."

Medical management might be more complicated for *C. gattii* compared to *C. neoformans*, including the possibility of azole drug resistance and the formation of cryptococcomas in the central nervous system that can be difficult to treat and that cause abscesses. "Based on the prevalence we found, it makes sense to pursue further clinical studies, not just to find out the species, but also the molecular type, so we can learn all we can about how this pathogen is travelling and evolving," Heitman said.

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**Novel method for increasing antibiotic yields**
A novel way of increasing the amounts of antibiotics produced by bacteria has been discovered that could markedly improve the yields of these important compounds in commercial production. It could also be valuable in helping to discover new compounds. With the ever-growing threat from antibiotic resistance, these tools will be very useful in ensuring that we have enough of these useful compounds in the future.

The majority of antibiotics we know of today are produced naturally by a group of soil bacteria called Streptomyces. For commercial production of these antibiotics for clinical use, it is necessary to increase the yield. This has typically been achieved by randomly inducing mutations and screening for strains that show increased production, a process that takes many years. When technology had progressed sufficiently
to analyse how this had been achieved scientists found that, in some cases, the increase in yield was due to repeated copies of the genes needed for antibiotic production.

In almost all cases, the genes needed to produce these antibiotics are clustered together in the bacterial genome. In work carried out initially at the John Innes Centre, which is strategically funded by the Biotechnology and Biological Sciences Research Council, Professor Mervyn Bibb and collaborator Dr Koji Yanai from a Japanese laboratory discovered 36 repeating copies of one gene cluster in a strain of Streptomyces that had been repeatedly selected to over-produce the antibiotic kanamycin.

"This suggested to us that controlled and stable amplification of antibiotic gene clusters might be possible, and that if it was, it would be a valuable tool for engineering high yielding commercial strains of bacteria," said Prof Bibb. The researchers then went on to identify the components within Streptomyces responsible for creating the 36 repeating clusters that led to kanamycin overproduction. These consist of two DNA sequences that flank the gene cluster, and a protein, known as ZouA, that recognises the two sequences and replicates them.

In research to be published in the journal Proceeding of the National Academy of Sciences, Prof Bibb and colleagues Dr Takeshi Murakami and Prof Charles Thompson, working at the University of British Columbia, together with the same Japanese pharmaceutical laboratory, describe a system for the targeted amplification of gene clusters. The researchers were able to engineer these components into genetic 'cassettes' and then insert these into another strain of Streptomyces. They successfully used the system to make Streptomyces coelicolor overproduce actinorhodin, a blue-pigmented antibiotic. They believe the system will work equally as well for many other Streptomyces strains and antibiotics, and have also shown that it functions in an unrelated bacterium, Escherichia coli.

The system may also uncover new, undiscovered antibiotics. A number of Streptomyces species have had their entire genomes sequenced, and many more are expected. Researchers have been able to identify other gene clusters within these sequences with unknown products. It is likely that many of these 'cryptic' gene clusters produce potentially new antibiotics, but at an undetectable level, or only under specific environmental conditions. Using the gene cluster amplification system identified here, it will be possible to amplify these cryptic gene clusters, identify their products, and potentially discover new antibiotics for the battle against resistant superbugs.

Co-infection with hepatitis delta increases risk of death for patients with HIV and chronic hepatitis B

Michael Carter
Published: 05 September 2011
Infection with hepatitis delta virus is associated with an increased risk of death for HIV-positive patients with chronic hepatitis B infection, European research published in the online edition of AIDS shows.

"In our study we reported for the first time that hepatitis delta was...predictive of increased risk of liver-related death and overall mortality in HIV patients," write the investigators, who recommend that all HIV-positive patients with chronic hepatitis B infection should be tested for the infection.

Hepatitis delta (HDV) is the most aggressive form of chronic hepatitis infection in humans. Worldwide, between 15 and 20 million individuals carry the virus, including 5% of patients with chronic hepatitis B virus infection (HBV).

HIV, hepatitis B, and hepatitis delta all share modes of transmission, including sex transmission, injecting drug use and from a mother to her baby.

However, little information is available on the prevalence of the infection in patients with HIV. Nor are its epidemiology, viral characteristics, and natural history well understood.

To answer these questions investigators from the EuroSIDA cohort examined the medical records of HIV-positive patients with chronic hepatitis B (hepatitis B surface antigen positive [HBsAg+]). Their analysis included 422 patients and 61 (15%) had antibodies to hepatitis delta.

Prevalence of the infection was significantly higher in patients with a history of injecting drug use (42%) compared to patients whose HIV risk factor was heterosexual intercourse (9%) or sex between men (3%) (p < 0.001).

Hepatitis delta co-infection was more common in Southern (21%) and Eastern Europe (9%) than in Northern (9%) or Central Europe (11%) (p = 0.003).

Most of the hepatitis delta-infected patients were white (84%) and two-thirds were receiving antiretroviral therapy. Median CD4 cell count was 281 cells/mm³ and median HIV viral load was undetectable.
The investigators' first set of analyses showed that co-infection with hepatitis delta was significantly associated with younger age (p = 0.0007), female sex (p = 0.005), intravenous drug use (p < 0.0001), co-infection with hepatitis C virus (p < 0.0001), residence in Southern or Eastern Europe (p < 0.003), and infection with hepatitis B sub-type D (p < 0.01).

However, only injecting drug use (p = 0.0003) remained significant in analysis that controlled for confounding factors.

Hepatitis B genotype D was detected in 50% of patients infected with hepatitis delta compared to 12% of individuals negative for the infection.

The investigators were able to detect hepatitis delta viral load in 31 patients, and median viral load was 1.76 x 10^7 copies/ml.

The only hepatitis B subtype found in patients with a hepatitis delta viral load above this level was subtype D.

Earlier research has shown that, with the exception of patients with hepatitis B subtype D, co-infection with hepatitis delta is associated with an attenuation of hepatitis B virus infection. The present study confirmed these findings. Overall, co-infected patients had lower median hepatitis B viral loads than patients not infected with hepatitis delta (p = 0.003). However, the exception was patients with hepatitis B genotype D.

“Hypothetically, this last group of patients replicating both HBV and HDV might experience enhanced liver damage,” suggest the investigators.

Co-infection with hepatitis delta was associated with an increased risk of death (p = 0.01) and of death from end-stage liver disease (p = 0.008).

Treatment for hepatitis delta is “challenging” and usually consists of twelve months of therapy with pegylated interferon-alpha. There is also some evidence that tenofovir, 3TC and adefovir are active against the virus.

“Most guidelines recommend that HBsAg+ patients should be tested for anti-HDV antibodies,” note the authors, “failure to exclude HDV infection in HBsAg carriers may result in an unexpected worse outcome and trigger unnecessary search for other etiologies of liver disease.”

Reference

Plasma and rectal viral load correlated in HIV-positive gay men: supports use of treatment as prevention
Michael Carter
Published: 06 September 2011
Viral load in the blood and rectal secretions of HIV-positive gay men are highly correlated, according to US research published in the September 1st edition of the Journal of Infectious Diseases. The study also showed that the presence of sexually transmitted infections did not increase rectal viral load.

Individuals with a plasma viral load above 1000 copies/ml were significantly more likely to have detectable virus in the rectum.

“Our data add substantially to the few published studies of HIV shedding in rectal secretions of MSM [men who have sex with men],” comment the investigators, “we were able to quantify HIV RNA in rectal secretions, demonstrate the linear correlation between increasing plasma load and rectal viral load and determine a threshold plasma viral load that distinguished detectable from undetectable rectal viral load.”

They also believe that their findings have important implications for current debates about the use of HIV treatment as prevention, commenting: “Combination antiretroviral therapy will have a similar effect on reducing HIV transmission in MSM, as seen in studies of heterosexual discordant couples.”

Gay men remain one of the groups most affected by HIV. Unprotected anal sex is the primary mode of HIV transmission for gay men, and it is estimated that 28% of infections in this population are due to insertive anal intercourse. Therefore, rectal secretions are an important potential source of HIV transmission. Moreover, gay men have a high incidence of bacterial sexually transmitted infections, and these have been shown to increase urethral HIV viral load.

However, the relationship between plasma and rectal viral load is poorly understood. Nor is the impact of sexually transmitted infections on rectal viral load well established.

Therefore investigators from the Study to Understand the Natural History of HIV in the Era of Effective Therapy (the “SUN” study) measured rectal viral load using samples collected via swabs used to
monitor patients for infection with gonorrhoea or chlamydia. The investigators paired rectal and plasma measurements of viral load.

The study involved 80 men, and 59 (74%) were taking antiretroviral therapy. The patients' median CD4 cell count was 467 cells/mm$^3$ and 63% had a plasma viral load below 1000 copies/ml.

Almost all the men (95%) had rectal human papilloma virus (HPV) infection, and two-thirds had herpes simplex virus. Rectal gonorrhoea or chlamydia was detected in 39% of men.

Rectal HIV was detected in 38% of men overall and in 42% of rectal samples.

Viral load in rectal samples and plasma were highly correlated. This included men with rectal sexually transmitted infections.

HIV was significantly less likely to be detected in the rectal samples of men who had a plasma viral load below 1000 copies compared to men with a blood viral load above that value (p < 0.001).

A lower CD4 cell count (p < 0.001) was also associated with detectable virus in the rectum, as was not taking HIV therapy (p < 0.001).

However, after controlling for potential confounders, the investigators found that the only factor associated with an increased risk of having detectable virus in the rectum was a plasma viral load above 1000 copies/ml (p = 0.008).

“We believe our findings demonstrate that among MSM receiving contemporary antiretroviral therapy, controlling plasma viral load is an important means (in fact, perhaps the most important) of reducing rectal viral load, underscoring the value of expanded use of early cART among HIV-infected MSM in the United States to reduce HIV transmission from exposure to rectal secretions,” comment the investigators.

The researchers also believe that taking HIV therapy “may mitigate the effect of STIs on HIV transmission from infected MSM to their uninfected partners.”

They conclude “our findings indicate that a low plasma HIV viral load is associated with a low HIV load in rectal secretions...these findings support the use of cART as an effective means of reducing HIV transmission among MSM in the United States by reducing the amount of virus shed in body sites where transmission occurs.”

Reference
Kelley CF et al. HIV-1 RNA rectal shedding is reduced in men with low plasma HIV-1 RNA viral loads and is not enhanced by sexually transmitted infections in the rectum. J Infect Dis 204: 761-67, 2011 (click here for the free abstract).

A victory for Novartis could spell death for millions
Priscilla Jebaraj

The Swiss pharma giant fighting in Supreme Court for patent on anti-cancer drug

A case being heard in the Supreme Court on Tuesday could signal a death sentence for Loon Gangte. Mr. Gangte is not accused of any crime. But he — and thousands of other HIV positive people — will be avidly following the Supreme court's hearing of the Novartis vs Union of India, Cancer Patients Aid Association & others, because if the Swiss pharmaceutical giant wins its case, the drugs that keep Mr. Gangte alive could become too expensive for him.

“For us, it’s about life and death,” Mr. Gangte said on the eve of the hearing. “We can’t let them win.”

In the latest battle of a six-year long war, Novartis has taken the Indian government to court, challenging the legal interpretation of a critical public health safeguard in the nation's patent law — Section 3(d) — that limits the patenting of new forms of old medicines. If Novartis wins, much of the Indian generic drug industry — which acts as the pharmacy for the entire developing world — could be in trouble.

The Swiss company is fighting for a patent on a new crystalline salt form of the anti-cancer drug imatinib mesylate, which it sells under the brand name 'Gleevec'. Since the original molecule is out of patent in India, generic drug companies produce and sell Gleevec to chronic myeloid leukemia patients for about Rs.8,000 per month, while Novartis sells the drug for about Rs.1.2 lakh per month. A patent on the new form could give Novartis a 20-year monopoly on the drug, thus “ever-greening” the patent.

In 2006, the Indian patent office ruled that the new salt form did not deserve a new patent, since it did not meet the provison of “increased efficacy” required under Sec. 3(d). Novartis argued that the salt form would have higher levels of availability in the body of the patient, but the Madras High Court clarified that “efficacy” means “therapeutic efficacy in healing a disease”. Having lost its case in the lower court, Novartis is now asking the Supreme Court to interpret “efficacy” in a way that will allow its patent.

So why does a case about an anti-cancer drug matter to an HIV positive person like Mr. Gangte?
“This is the first such case to reach the Supreme Court, and it’s being viewed as a test case by the industry,” says Amit Sen Gupta of the People’s Health Movement. “It would open a Pandora’s Box.”

Patent applications for a number of other drugs, including treatments for HIV/AIDS and tuberculosis, have been withdrawn or denied on the basis of Sec 3(d). If the provision is diluted, the cost for these treatments could shoot up by up to 40 times, making them unaffordable for the majority of patients.

“I was diagnosed in 1997, but I could not afford treatment at all until the Indian generic drugs started becoming available four years later,” says Mr. Gangte, who is secretary of the Delhi Network of Positive People. “The government started its own free HIV treatment programme in 2004, once cheaper generics were freely available.

It is not just Indian patients who are worried. “About 80 per cent of anti-AIDS drugs and 92 per cent of drugs to treat children with AIDS across the developing world comes from the Indian generic manufacturers,” says Leena Menghaney of Medecins Sans Frontieres (translated from French as Doctors Without Borders). “India is literally the lifeline of patients in the developing world, especially in the poorest parts of Africa...If Sec. 3(d) is overturned, it means any meaningful effort to make these vital medicines available will be put in jeopardy.”

“When I look through my photo albums from the early years, I can see that almost all those friends are now dead,” says Mr. Gangte. “I hope the Supreme Court does not condemn us all.”

05 September 2011

Zimbabwe’s Mugabe Urges Stronger Male Role in Fighting HIV Transmission

Mr. Mugabe told the four-day conference that the transmission of HIV is a global injustice that must be eliminated, and that the large number of children living with HIV calls the nation to more intense and effective action.

Zimbabwe President Robert Mugabe on Monday opened a national HIV and AIDS conference with a call for the nation's men to take a larger role in the response to the deadly pandemic, not only for their own health but that of women and children.

In his keynote speech, Mr. Mugabe told the four-day conference that the transmission of HIV is a global injustice that must be eliminated, and that the large number of children living with HIV calls the nation to more intense and effective action.

The focus of the conference will be improved prevention of mother-to-child transmission of HIV. One of Zimbabwe’s 2015 Millennium Development Goals is to reduce mother-to-infant transmission to 5 percent of births from around 25 percent today.

About 15,000 Zimbabwean newborns are infected each year with the AIDS virus.

Current World Health Organization guidelines state that a pregnant mother who tests positive for HIV should start taking a preventive medicine known as Zidovudine at about 14 weeks until the onset of labor to protect the baby from being infected.

National Director Lindiwe Chaza-Jangira of the Zimbabwe AIDS Network said she welcomed the call by President Mugabe for an expanded male role in the battle against AIDS—something that community health workers have long advocated, she said.

Chaza-Jangira said male partners must be more involved in understanding and supporting measures to prevent mother-to-child transmission, and basic HIV/AIDS prevention.

Elizabeth Mazhetese, operations director for the HIV/AIDS Zimbabwe Charity, said HIV transmission from mother to child continues in large part due to the stigma attached to HIV-positive status which discourages expectant mothers from seeking help.

She said women often worry about the response from husbands and family to news they are HIV-positive, a dynamic health workers are working to overcome.

Does CD8 Cell Activation Affect CD4 Cell Recovery on ART?

Published on Tuesday, 06 September 2011 00:00
Written by Liz Highleyman
Greater activation of CD8 "killer" T-cells was associated with smaller gains in CD4 "helper" T-cells among people in Uganda who achieved good HIV viral load suppression on antiretroviral therapy (ART), researchers reported in the August 30, 2011, advance online edition of AIDS.

A growing body of evidence suggests that excessive immune activation and inflammation contribute to the elevated risk of non-AIDS conditions such as cardiovascular disease, neurocognitive impairment,
and bone loss in people with HIV. Chronic activation is also thought to "wear out" or contribute to accelerated aging of the immune system.

Peter Hunt and Steven Deeks from the University of California at San Francisco and colleagues looked at the effect of T-cell activation on CD4 cell recovery and mortality in a resource-limited setting.

Immune activation is associated with poor CD4 cell recovery among people in resource-rich settings, the authors noted, but "little is known about its prognostic importance in resource-limited settings, where differences in host genetics, viral factors, and prevalent co-infections may modify these associations."

This prospective study included 451 HIV positive participants in the Uganda AIDS Rural Treatment Outcomes (UARTO) cohort in Mbarara who started combination antiretroviral treatment. Most (70%) were women, the median age was 34 years, the median baseline CD4 count was 135 cells/mm³, and the median baseline viral load was about 125,000 copies/mL.

Every 3 months the researchers measured viral load, CD4 cell count, and percentage of activated T-cells, indicated by the presence of the cell surface markers CD38 and HLA-DR. The median follow-up period was 24 months; 8% of participants were lost to follow-up at 3 years.

**Results**

- Most participants (93%) achieved plasma viral load < 400 copies/mL by 6 months and were included in further analysis.
- Higher pre-treatment CD8 T-cell activation was significantly associated with smaller CD4 cell gains at 1 year, after adjusting for sex and pre-treatment CD4 count and viral load (P=0.017).
- CD8 T-cell activation at 1 year showed a trend toward slower CD4 cell recovery, but the difference did not reach statistical significance.
- 34 participants died during follow-up, 15 of them after 6 months on ART.
- Each 10% increase in activated CD8 T-cells at month 6 on ART was associated with a 1.6-fold increased risk of death, after adjusting for pretreatment CD4 count (P = 0.48).

Based on these findings, the study authors concluded, "Higher pre-ART CD8+ T-cell activation independently predicts slower CD4+ T-cell recovery and higher persistent CD8+ T-cell activation during ART-mediated viral suppression independently predicts increased mortality among HIV-infected Ugandans."

HIV negative people living in resource-limited settings in sub-Saharan Africa are known to have a higher proportion of activated T-cells than those living in resource-rich settings, they explained in their discussion. These differences have been attributed to environmental factors such as helminth (worm) and malaria infections.

At the 2010 Conference on Retroviruses and Opportunistic Infections, Hunt's team presented earlier data from this cohort showing that Ugandans had a higher level of CD8 T-cell activation, on average, than HIV positive participants in a San Francisco cohort. The Ugandans saw a decline in CD8 cell activation after starting ART, but it remained above that of the San Francisco group.

"[W]e have established for the first time that higher persistent CD8+ T-cell activation during early viral suppression independently predicts subsequent mortality in this setting, suggesting that immune activation is a major determinant of clinical outcomes in resource-limited settings," the authors continued in their discussion. "While low pre-therapy CD4+ T-cell counts remains the strongest predictor of overall mortality in HIV-infected Ugandans, high persistent CD8+ T-cell activation during suppressive ART is a more significant predictor of deaths occurring after the first 6 months of therapy."

"We also found that higher pre-treatment [CD8+] T-cell activation and lower pre-treatment CD4+ T cell counts strongly predicted higher T-cell activation during suppressive ART," they continued. "This is an important observation as it may suggest an immunologic cost to delaying ART initiation in this setting."

"The fact that pre-treatment T-cell activation strongly predicts T-cell activation levels during suppressive ART also suggests that factors other than the extent of productive HIV replication are likely to contribute to T-cell activation both in the presence and absence of suppressive ART," the authors explained. "Studies in both resource-rich and resource-limited settings suggest that residual T-cell activation during ART-mediated viral suppression may be at least partly explained by persistently abnormal levels of microbial translocation [leakage of bacteria from the gut] and other chronic coinfections including CMV and/or other herperviruses."

"[I]nterventions designed to further reduce immune activation in this setting should be studied," they recommended. "Given the strong relationship between lower pre- treatment CD4+ T cell count and higher residual T cell activation, these observations also support the earlier initiation of ART in this setting."
New Swine Flu Viruses Identified in 2 Children in U.S.

Published on Tuesday, 06 September 2011 00:00

Written by Liz Highleyman

Swine flu © Russell Kightley

Last month 2 children in Indiana and Pennsylvania were diagnosed with novel strains of swine-origin influenza A (H3N2), according to a September 2, 2011, early online edition of the CDC's *Morbidity and Mortality Weekly Report*. Both children with the virus—which is distinct from the H1N1 pandemic influenza A identified in 2009—had fevers and other typical flu symptoms, but recovered without complications.

Influenza A viruses are endemic in many species, including humans, swine, and wild birds, and sporadic cases of transmission of between humans and animals can occur, the report authors noted as background. Genetic analysis can distinguish animal-origin flu viruses from typical seasonal human influenza viruses that cause annual epidemics.

The report describes 2 cases of febrile respiratory illness caused by swine-origin influenza A (H3N2) identified on August 19 and August 26. The first case involved a boy younger than 5 years in Indiana. He experienced fever, cough, shortness of breath, diarrhea, and sore throat on July 23 and was taken to a local emergency department. The child was discharged without antiviral treatment but returned to the ED the next day and was hospitalized for pre-existing chronic health problems; he was again sent home on July 27 and has since recovered from this illness. After a respiratory specimen tested positive for influenza A (H3), the Indiana State Department of Health identified a suspect swine-origin influenza A (H3N2) virus on August 17, which was confirmed by the CDC on August 19.

While the boy had no known direct exposure to pigs, a caretaker who provided care 2 days before the boy became ill did report direct contact with asymptomatic swine in the preceding weeks. Neither the caretaker nor any member of the boy's family nor any close contacts have since developed respiratory illness.

The second case involved a girl, also younger than 5, in Pennsylvania. This child experienced acute onset of fever, nonproductive cough, and lethargy on August 20. She too was taken to a local hospital ED, tested positive for influenza A, and was discharged the same day with no antiviral therapy. The girl has since completely recovered from this illness. On August 23 the Pennsylvania State Department of Health identified a suspected swine-origin influenza A (H3N2) virus, which was confirmed by the CDC on August 26.

The girl had visited an agricultural fair on August 16, where she had direct exposure to pigs and other animals. As with the previous case, none of her family members or close contacts has since come down with a similar illness, though the health department is investigating whether other fair-goers might have been infected.

Public health officials have not identified any epidemiologic link between the Indiana boy and the Pennsylvania girl. Genetic sequencing revealed that the viruses are similar to each other, but not identical. Out of 8 flu genes, 7 are similar to those of swine H3N2 influenza A viruses circulating among pigs in the U.S. since 1998, which have been responsible for 8 other swine flu infections in humans since 2009.

The 1 difference is a matrix gene acquired from the 2009 influenza A (H1N1) virus, which is thought to have been transmitted from humans to pigs. This particular genetic combination is unique and has not been reported previously in either swine or humans, according to the report authors. Genotypic testing indicates that the newly identified H3N2 viruses are resistant to amantadine (Symmetrel) and rimantadine (Flumadine), but susceptible to oseltamivir (Tamiflu) and zanamivir (Relenza).

According to an editorial note, the CDC has received 3-5 reports of human swine flu infection per year since 2007. Between December 2005 and November 2010 there were 21 reported cases of human infection with swine-origin flu viruses: 12 with influenza A (H1N1), 8 with influenza A (H3N2), and 1 with influenza A (H1N2). Only 6 of these 21 cases occurred in people known to have direct exposure to pigs, 12 reported being near pigs, and 2 cases had contact with another ill person who had exposure with pigs, suggesting probable human-to-human transmission.

"Although the vast majority of human infections with animal influenza viruses do not result in human-to-human transmission, each case should be investigated fully to ascertain whether these viruses
are transmitted among humans and to limit further exposure of humans to infected animals, if infected animals are identified," the authors wrote.

"Clinicians should consider swine-origin influenza A virus infection as well as seasonal influenza virus infections in the differential diagnosis of patients with febrile respiratory illness who have been near pigs," the editorial advised.

"Non-human influenza virus infections rarely result in human-to-human transmission, but the implications of sustained ongoing transmission between humans is potentially severe; therefore, prompt and thorough identification and investigation of these sporadic human infections with non-human influenza viruses are needed to reduce the risk for sustained transmission," the report concludes.

Reference

'No Evidence' Mutant Bird Flu Virus Poses Increased Risk To Humans, WHO And FAO Say

After the U.N. Food and Agriculture Organization (FAO) "last week voiced concern about the appearance in Vietnam and China of" a mutant strain of the H5N1 bird flu virus, the WHO and FAO on Monday "said in a joint statement issued in response to questions from Agence France-Presse" that "[t]here is no evidence to suggest yet that this new virus strain will have any increased risk to human health," the news agency reports. "Nevertheless, poultry producers and the general public should always take simple precautions to reduce exposure to the virus from infected poultry," it said," the news agency writes, noting the "H5N1 virus typically spreads from birds to humans via direct contact" (9/5).

Number Of Malaria Cases In Brazilian Amazon Drop 31% In First Half Of Year Compared With 2010

Brazil's health ministry on Monday said 115,708 malaria cases had been reported in the first half of this year in the Brazilian Amazon, down 31 percent compared with the same period in 2010, the Latin American Herald Tribune reports. "'The positive figures are the result of comprehensive action, which includes stepping up the routines for early diagnosis and the opportune treatment of patients,' Health Minister Alexandre Padilha said," the newspaper writes.

The ministry launched a campaign on Monday to distribute 1.1 million insecticide-treated bed nets with the objective of 'close[ing] the year with less than 300,000 cases of malaria, a 'daring' goal since most of the infections occur in the month of August, Padilha told the official Agencia Brasil news agency," according to the newspaper (9/6).

Major advance in sleeping sickness drug made by Glasgow scientists ***

A new study published in the open-access journal PLoS Neglected Tropical Diseases on September 6th presents a key advance in developing a safer cure for sleeping sickness. Led by Professor Peter Kennedy, researchers at the University of Glasgow's Institute for Infection, Immunology and Inflammation have created a version of the drug most commonly used to treat sleeping sickness which can be administered orally in pill form.

Sleeping sickness – or human African trypanosomiasis (HAT) – is a neglected tropical disease of major importance. Transmitted by the tsetse fly and caused by the trypanosome parasite, sleeping sickness is invariably fatal if left untreated. Once the disease has crossed the blood-brain barrier and entered the central nervous system the most commonly used treatment is an intravenous course of the arsenic-based drug melarsoprol. Because melarsoprol has a low solubility in water, it is dissolved in propylene glycol and administered intravenously. The result is a highly-toxic drug that kills five per cent of patients receiving it and leaves many others permanently brain-damaged.

Researchers at the University of Glasgow combined melarsoprol with cyclodextrins – molecules that surrounded the drug allowing it to be administered orally, increasing its solubility and releasing the drug more slowly in the gut. In laboratory tests the altered drug was shown to retain its ability to kill the infection, and was able to cure mice infected with the parasite after a seven-day daily oral dosing schedule. The drug cleared parasites from the brain and restored normal blood-brain barrier integrity.

According to Prof. Kennedy, "This new research is the most clinically important in the 20 years of our trypanosome research group. It has the potential of a major therapeutic advance and if it is equally
effective in humans then it would also have a significant socio-economic impact because the duration of inpatient treatment would be shorter and some patients might even be eventually treated at home."

Prof Kennedy added: "You always have to be very cautious when extrapolating results from mouse models to the human disease but there are several reasons why we are quietly optimistic that this may very well work in humans too.

New HIV Vaccine Approach Targets Desirable Immune Cells
ScienceDaily (Sep. 6, 2011) — Researchers at Duke University Medical Center, Beth Israel Deaconess Medical Center and Harvard Medical School have demonstrated an approach to HIV vaccine design that uses an altered form of HIV's outer coating or envelope protein.

The researchers showed that they could design HIV envelopes that could bind better to immature B cell receptors to create an enhanced immune response in an animal model. Immature B cells are the targets of vaccines, and when strongly targeted, they produce strong vaccine responses. The work of the Duke team was to improve on the ability of the HIV envelope to target immature B cells of the immune system.

"This is first step towards a new way of making vaccines against HIV: targeting immature immune cells and attempting to drive a pathway of events that rarely occur," said Barton Haynes, M.D., co-senior author and director of the national Center for HIV-AIDS Vaccine Immunology (CHAVI) laboratory and Frederic M. Hanes Professor of Medicine and Immunology at Duke University School of Medicine. "This avenue of research provides additional evidence about why some of the earlier, traditional vaccine approaches for HIV may not have been successful."

The study was published in the Sept. 1 issue of PLoS Pathogens.

Handcrafting vaccines that will stimulate different stages of the pathway toward immunity looks to be important, Haynes said. A vaccine usually uses a part of the virus (like part of its outer coating) or a harmless form of the virus to create a strong immune response against the virus.

This new work is the first time researchers have made an HIV envelope that binds better to precursor antibodies and also stimulates better immunity, compared with a natural envelope, in primates.

Hua-Xin Liao, M.D., Ph.D., a professor of medicine in the Duke Human Vaccine Institute (DHVI) and co-senior author, created the altered HIV outer coats. "Roadblocks thrown up by HIV have plagued HIV vaccine development," Liao said. "HIV hides its Achilles' heels of vulnerability on its outer coat by covering them with sugars. This covering is the result of virus mutations as the virus became resistant to antibodies."

The researchers found that the sugars on the natural HIV envelope prevented the envelope from binding to the immature B cell receptors that scientists want to trigger with a vaccine. So human and animal B cells fail to make antibodies against the HIV envelope's vulnerable spots when natural HIV envelope is injected as a vaccine candidate, even though these viral envelopes are the target of protective, neutralizing antibodies.

"We found that when you remove the sugars from the envelope proteins, you can create an envelope that targets those immature B cell receptors," said Haynes, who is also director of the DHVI.

"After the initial results, we completed a study in primates, which are similar to humans in terms of their genetics and their immune systems," Haynes said. "When they were given the HIV outer coat with many of the sugars removed, this sugar-depleted envelope bound better to the immature B cell receptors and stimulated antibodies better, which is a first step in the HIV-1 envelope activating an immature B cell target that previously it could not target."

Dimiter Dimitrov at the National Cancer Institute has previously shown that the natural HIV envelope protein frequently does not target immature B cells.

"The importance of this new finding is that it not only provides evidence for our hypothesis, but also for the first time it has identified envelope-based immunogens capable of binding to putative antibody germline predecessors that correlated with enhanced immunogenicity in animals," Dimitrov said.

Investigators have found that pathways for inducing the "right" kind of antibodies may be blocked or are unusual and are not routinely followed by HIV envelope-induced antibodies. John Mascola, Peter Kwong and colleagues at the Vaccine Research Center of the National Institute of Allergy and Infectious Diseases (NIAID) have shown that very complex, broadly neutralizing B cell maturation pathways may require targeting early B cell receptors.

"This is an important step forward," said Nelson Michael, director of the Military HIV Research Program at the Walter Reed Army Institute of Research. "The observation that improving envelope
immunogen binding to immature B cell receptors can improve immunogenicity provides new hope for design of strategies for inducing difficult-to-induce neutralizing antibodies.”

Journal Reference:

Crowd-Sourcing the E. Coli O104:H4 Outbreak

ScienceDaily (Sep. 4, 2011) — Ten variants of the deadly Escherichia coli strain that hit Germany in May 2011 have been sequenced across the world. The unprecedented level of collaboration across the scientific community should give insight into how the outbreak arose, says a scientist at the Society for General Microbiology’s Autumn Conference 2011.

Sequencing of the bacterium started in early June at BGI, China. Their sequence was provided in draft form to the scientific community as a crowd-sourcing project. This allowed scientists, including those at The Genome Analysis Centre (TGAC) in Norwich to identify key disease-causing genes. Dr Lisa Crossman, Microbial Genome Project Leader at TGAC, explained, "We have found that the E. coli strain responsible for the outbreak carries a very high number of genes known to be involved in disease. These include genes that influence the bacterium’s ability to attach to surfaces and survival genes that increase tolerance to high acidity, low oxygen, UV light and antibiotics."

The outbreak of E. coli O104:H4 resulted in a large number of cases of bloody diarrhea and haemolytic uremic syndrome (HUS) in Germany, and in 15 other countries in Europe and North America. The earliest studies suggested contaminated cucumbers were to blame. However by 10 June, raw beansprouts were identified as the source of infection. Over 4,000 cases and around 50 deaths have occurred so far across 16 countries in Europe and North America. The outbreak has also had a very high economic impact on the fresh vegetable market, especially in Spain and across Europe.

Crowd-sourcing researchers found that the outbreak strain is most closely related to a strain of E. coli originally isolated in Central Africa some years ago, which was responsible for cases of serious diarrhea. "The E. coli O104:H4 outbreak strain has gained the ability to make a toxin from a bacterial virus source which has made it more dangerous," explained Dr Crossman.

The unprecedented global crowd-sourcing effort meant that in the very immediate term, doctors were able to distinguish this strain from others, said Dr Crossman. "Knowing which antibiotic resistance genes are carried by the strain, for example, can provide us with more insight into the source of the outbreak and help us avoid similar outbreaks occurring in the future," she said.
Institutions around the world have now isolated ten different variants of E. coli O104:H4. "These variants represent a tremendous resource to examine this bug in a new, rapid and exciting way. By studying the genetic factors involved in the survival of this bacterium on surfaces, we hope to get an angle on how this organism has been able to get a foothold in the global food chain," suggested Dr Crossman.

**Scientists Discover Secret Life of Chromatin: DNA/Histone Combination, a Destination for Cell Signals, Also Talks to Other Proteins**

ScienceDaily (Sep. 6, 2011) — Chromatin—the intertwined histone proteins and DNA that make up chromosomes—constantly receives messages that pour in from a cell's intricate signaling networks: Turn that gene on. Stifle that one.

But chromatin also talks back, scientists at The University of Texas MD Anderson Cancer Center report in the journal *Cell*, issuing orders affecting a protein that has nothing to do with chromatin's central role in gene transcription—the first step in protein formation.

"Our findings indicate chromatin might have another life as a direct signaling molecule, that it can signal back to other proteins irrespective of gene transcription," senior author Sharon Dent, Ph.D., professor and chair of MD Anderson's Department of Molecular Carcinogenesis and director of the Center for Cancer Epigenetics.

In a series of yeast experiments, Dent and colleagues show that a signal through a histone protein regulates another protein called Dam1 that is involved in the separation of chromosomes during cell division.

**Signaling cascades don't dead-end at DNA**

"It's a basic change in our way of thinking about cell signaling—that all signals go into the nucleus and dead-end at DNA, that they point to chromatin and stop," Dent said. "Our data show that's not the case. We have a new fundamental aspect of cellular regulation that we need to now explore." DNA is tightly intertwined with histones and assembled in histone/DNA units called nucleosomes along the connecting length of a string of DNA. This structure is often described as being like beads on a string.

Genes are turned on by transcription factors, proteins that attach to the gene's promoter region and order the gene to make an RNA copy of its DNA that can be translated into a protein. Histone proteins regulate access to genes, blocking or facilitating transcription.

Histones and other proteins are modified by the attachment of chemical groups to specific spots on the protein. Attachment of a methyl group (a carbon atom joined to three hydrogen atoms) to a histone can help or hinder gene transcription depending on where the methylation occurs on the histone, Dent said.

**Crucial cross-talk between proteins**

In a 2005 Cell paper, Dent and colleagues reported that a methyl group-transferring protein called Set1 methylates the protein Dam1, which is part of a structure that assists in the orderly separation of chromosomes during cell division.

Set1 is part of a protein complex that works along with multiple regulatory factors to facilitate transcription by attaching methyl groups to a specific histone, H3, which was the only previously known target of Set1.

Dent's team set out to discover the exact mechanism by which Set1 methylates Dam1. To their surprise, they found that Dam1 methylation does not depend on gene transcription, revealing news roles for proteins formerly thought to be involved only in that process.

Rather, the crucial step is the attachment of a single signaling molecule called ubiquitin to a histone protein called H2B. This event was known to direct addition of methyl groups to histone H3, but Dent's work indicates it is also required for methylation of Dam1.

Communication between H2B and Dam1 is the first such instance of cross-talk between histone and non-histone proteins, the authors report. The signaling connection between a chromatin change and a non-DNA-templated process such as chromosome separation is also new.

Connections between histone ubiquitination and histone methylation also occur in human cells, and mutations in a protein highly related to Set1, called MLL, are involved in leukemia. Dent's work raises the possibility that histones can signal to non-histone proteins in human cells and that mismanagement of these events caused by MLL mutations might contribute to leukemia development.

Dent's group is looking for other proteins that might be affected by histone modifications in both yeast and human cells. And they are studying the details of Dam1 methylation and its function in chromosome separation.
Journal Reference:

Fluctuating symptoms have major impact on quality of life and fitness to work, survey finds
Gus Cairns
Published: 07 September 2011
Common but non-specific symptoms of uncertain cause can dominate the day-to-day life of some people with HIV, a survey by the National AIDS Trust has found. In many cases symptoms such as fatigue, insomnia, depression, diarrhoea and neuropathy make it hard to work and perform other daily activities, the report of the survey finds.

The survey also found a significant degree of overlap between symptoms; generally, if people had one symptom, more than two-thirds of them were likely to have at least one other. One other finding was that the majority of respondents found that the symptoms were not only fluctuating, but were also completely unpredictable. This made planned activities, both at work and socially, difficult. About 60% of respondents were employed.

This study is a pilot survey of an independent working group brought together to review the Work Capability Assessment (WCA), the medical procedure under which claimants are assessed for Employment and Support Allowance. The WCA had been criticised, especially in an independent review conducted by occupational health expert Professor Malcolm Harrington, for being inflexible and for not being designed to accommodate illnesses characterised by fluctuating symptoms. See www.aidsmap.com/Whats-happening-to-benefits/page/1793223/ for more on the WCA and the Harrington Report.

Survey results in detail
The NAT study asked people with HIV to complete an online survey about their experience, during the previous six months, of five symptoms commonly associated with HIV: fatigue, anxiety or depression, insomnia, gastro-intestinal problems and neuropathy (nerve pain). There was space to mention other symptoms too.

It is not surprising that in a study inviting people to self-report, the majority of the 265 respondents had at least one of the symptoms on the list. The most common was fatigue, suffered by 57%, followed by depression or anxiety (55%), gastro-intestinal (GI) problems (48%), insomnia (46%) and neuropathy (33%).

More significant was the fact that more people experienced these symptoms as fluctuating rather than constant. Respondents described conditions as 'constant' with frequencies ranging from about 38% in insomnia to 24% in the case of GI problems, but as 'varying over time' with frequencies ranging from 53% in fatigue to 31% with neuropathy.

Fatigue was mentioned as a particularly common and troubling symptom. Very few respondents could usually predict when fatigue would hit them. One commented that "When I have it I am quite incapacitated and have no choice but to limit, stop or cancel plans to do things." Another said "it is always there, lurking...if I do anything for more than an hour it begins to kick in." One respondent managed to hold down a job but always required a nap of one to two hours immediately after coming home. Although 40% of respondents thought a combination of HIV and HIV medications caused their fatigue, 30% said they really had 'no idea' what caused it.

Depression and anxiety were nearly as common as fatigue, though respondents did not say they affected work so much. The main feature of these were their frequency: 90% of respondents said they had experienced either or both at some point in the last month. Given that a third of respondents said that bouts of depression or anxiety lasted more than a week at a time, many people must be living with severely disordered mood a lot of the time.

Diarrhoea, nausea and other GI problems were the symptoms most likely to be linked in people's minds to HIV treatment. Thirty per cent of respondents thought these were the exclusive cause of their problems and 45% thought HIV and HIV treatments were both to blame. The frequency of bouts of diarrhoea varied from once to more than five times a month.

Insomnia and poor sleep, especially chronic, not only impacts on quality of life: it is a cause of significant physical and psychological illness. Although this has been associated with HIV drugs, especially efavirenz, 45% of respondents did not know why their sleep was so poor. Sleeplessness was very
unpredictable — people would be fine one night and not the next. Forty-three per cent said having problems sleeping could last for more than a week. When insomnia is this prolonged, memory, mood and cognitive function can be severely affected. One respondent said sleep problems meant “I am unable to focus on my work, feeling like I have jet lag.”

Neuropathy (nerve pain) was the least-experienced of the conditions but was still suffered by a third of respondents. About equal numbers of people attributed it to HIV itself and to HIV drugs. In some cases the pain of neuropathy was constant — one person said his feet were always sore and this prevented standing or walking for more than 15 minutes. But the majority said that while some symptoms such as numbness were always there others, such as stabbing pains, were unpredictable and often severe.

Most respondents suffered from multiple symptoms: for instance, of those with depression or anxiety, 75% also had fatigue and 57% insomnia; of those with neuropathy, 61% had fatigue and 68% GI problems.

About 40% of respondents were unemployed, with a higher proportion among those reporting GI problems or fluctuating neuropathy. There was a generally positive attitude to work, with one respondent happy to have just started a job after 18 months of unemployment — “I am knackered but happy to be working,” s/he said.

In other cases however it was clear that fluctuating symptoms were significantly affecting people’s ability or willingness to work. One question asked “on how many occasions in the past four weeks have your symptoms significantly affected your ability to work”? A quarter of people with fatigue, 20% with neuropathy, and about 15% of those with depression and GI problems reported that this had happened more than five times in the past four weeks.

One respondent asked: “How do you work round this kind of thing unless you work for yourself or for an extremely understanding employer?”

**Conclusions and recommendations**

NAT concludes that the responses to their survey reveal that fluctuating symptoms are a cause of real morbidity and distress to people living with HIV and place significant barriers to work. They add that the variation and unpredictability of symptoms was often as much of a problem as the symptoms themselves.

Because the symptoms are fluctuating, ESAs may not capture them if the person is having a ‘good day’, but there are other methods of assessment, such as asking people to keep a symptom diary.

NAT recommends that more research needs to be undertaken into these common, fluctuating symptoms and that HIV organisations should raise awareness amongst employers, and with people with HIV themselves, about the importance of making reasonable adjustments at work to enable people with HIV to continue in employment.

In terms of the ESA itself, NAT recommends that ESAs need to take into account “the full range of barriers fluctuating symptoms present to participation in work and other daily activities,” including their unpredictability and the fact that they come in combination.

“Assessment should consider the impact of fluctuation and the cumulative impact of multiple, lower-level symptoms on people living with HIV,” they comment.

**Reference**

The NAT Report *Fluctuating Symptoms of HIV* can be downloaded [here](#).

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**Sexual Pleasure Called Key to HIV-Gel Efficacy**

By Amy Littlefield

WeNews correspondent

Wednesday, September 7, 2011

*After decades of research, vaginal microbicides that prevent HIV infection are on the horizon. To fulfill their medical promise, a Rhode Island researcher says users’ sexual pleasure must be considered.*

PROVIDENCE, Rhode Island (WOMENSENEWS)—Participants in Kate Morrow’s recent study may not have felt like they were fighting the global HIV epidemic.

In fact, what they were literally feeling were gels of various consistencies inside their vaginas.

The women in Morrow’s Project LINK answered questions after handling the gels, inserting them vaginally, walking around and simulating intercourse with a fake phallus. Did the gel leak out? Did it inhibit the experience . . . or did they actually enjoy it?

Morrow has developed a set of scales to show the range of sensations and experiences women reported. Her goal now is to connect those sensations to data about which gels women would use to prevent HIV. Do they prefer gels that are smooth, thin or thick like hair gel? The answers to those questions could help lead to a microbicide that women will tolerate—and perhaps even enjoy.
For decades, women’s health advocates have known that women need a way to protect themselves from HIV that is not dependent on a male partner. Vaginal microbicide gels are among an array of options—including pills, rectal microbicides and vaginal rings—that may one day help. Advocates hope microbicides could even be combined with birth control and help prevent other sexually-transmitted illnesses.

That call is urgent today, with women worldwide making up just over half of new HIV infections among people over 15 in 2009, according to the most recent data from UNAIDS.

In the United States, 23 percent of people newly infected with HIV in 2009 were women. Black women were disproportionately affected, becoming infected at 15 times the rate of white women, and more than three times that of Hispanic/Latina women, according to the Centers for Disease Control and Prevention.

In sub-Saharan Africa, 60 percent of people living with HIV are women and girls, and young women ages 15-24 are as many as eight times more likely to be HIV positive than men, according to UNAIDS. Of those living with HIV worldwide in 2009, 34 percent lived in 10 countries in southern Africa.

Acceptability a Must
Researchers knew when they began creating microbicide gels that women could insert vaginally to prevent HIV that acceptability was a key question. If women weren’t willing to use them, the products wouldn’t work.

So Morrow, a staff psychologist at the Miriam Hospital here and an associate professor of research at the Alpert Medical School of Brown University, has been studying the nitty-gritty aspects of acceptability.

Funded by a grant from the National Institutes of Health, Project LINK began in 2006 and has examined about 350 women’s experiences of vaginal gels—none of which actually contained drugs. Data collection is complete and Morrow hopes to have results in the next year.

Those results could help determine what properties would make women willing—or even eager—to use a vaginal microbicide.

But there is no simple answer. Women’s responses to the gel could depend on how old they are, where they are in their menstrual cycles or whether they are bothered by things like leakage and stickiness. "How do I make this product feel good enough—or not feel like anything—such that women can use it without interrupting their normal day-to-day sexual lives? Or could it actually make their sexual lives better?" asked Morrow.

Studying pleasure is not something Morrow does for fun. She sees it as a "medical necessity" for preventing the spread of HIV. Even a partially-effective microbicide that is pleasant enough to gain wide use could dramatically reduce new infections. And a highly effective microbicide that women refuse to use won’t work at all.

Pleasure Integral to Health
Anna Forbes is former deputy director of the Global Campaign for Microbicides, an advocacy group with staff in Washington, D.C., South Africa, Zambia and Kenya. She said that understanding sexual pleasure is integral to public health because it affects real-world behavior, such as the refusal of some men to wear condoms.

"If you don’t talk about what people do for pleasure and what people do sexually, you’re cutting off your nose to spite your face in terms of HIV prevention," said Forbes.

For microbicides to catch on in a big way, Forbes said researchers may also have to persuade pharmaceutical companies—so far hesitant to invest—that microbicides are profitable. That could mean showing that U.S. women are willing to use microbicides—and pay for them.

Last year, researchers revealed that a vaginal gel containing the antiretroviral drug tenofovir reduced HIV incidence by 39 percent among women in South Africa who received it, compared to a placebo group. This CAPRISA 004 study was the first time researchers had shown a vaginal gel could reduce the spread of HIV. The gel also proved 51 percent effective in reducing the spread of genital herpes (HSV-2), which has been linked to a higher risk of HIV infection.

Women in the study were asked to insert the gel up to 12 hours before sex and as soon as possible within 12 hours after sex. The gel was more effective the more often it was used. Women who used it more than 80 percent of the time experienced a 54 percent reduction in HIV infection, versus 28 percent for women who used it less than half the time.

Consideration of Male Partners
Male partners might be unaware, accepting or even excited about the product—in any case, their experiences must be considered, said Morrow. While some women might discuss microbicide use with a partner, others might not be able to do so.
Morrow began another National Institutes of Health-funded study, Project MIST, in 2011 to examine how heterosexual couples experience vaginal products. She hopes to collect data from 24 couples by the end of the year.

Participants in both studies have received compensation.

In multi-site studies, women’s excitement over vaginal products has varied, depending on how real HIV is in their lives, Morrow said; the higher the sense of risk, the greater the motivation to try a vaginal gel.

While gel preferences may vary from place to place, the opinions of women in the United States who feel less at risk for HIV could help researchers develop optimum products for women in parts of the world where the disease risk is highest.

It could take years for a microbicide to become publicly available, but Morrow is dreaming of the day when her data might be an important part of the global anti-HIV solution.

"Can you imagine, 15 years from now, there’s some big New York Times headline that says the incidence for HIV in South Africa has dropped by 50 percent thanks to X, Y and Z microbicides, and you can sit here in little old Providence, Rhode Island, and say I was a part of that?" she said.

**Gay sex shouldn’t be illegal, says Ghana’s Minister for Justice**

In a surprising public statement, Ghana’s Minister for Justice—Martin Amidu—has said that gay sex should not be criminalised.

Peter Lloyd

7 September 2011

In a surprising public statement, Ghana’s Minister for Justice—Martin Amidu—has said that gay sex should not be criminalised.

The attorney general for the west African nation, who is also a National Democratic Congress party member, made the comment at a press event in Accra, last week.

"It is illegal to invade the privacy of two rightful-thinking adults to obtain evidence for prosecution purpose," he said.

Such public support for homosexuality there is rare and, according to AllAfrica.com, Amidu has "courted the wrath of anti-gay sections of the Ghanaian public" for voicing his opinion.

But equality activists have praised him for his honesty.

Despite this, Amidu added that he could not see homosexuality becoming full legal in Ghana in the near future.

**Gays, Lesbians Lose Out in Med School Curricula**

By Michael Smith, North American Correspondent, MedPage Today

Published: September 07, 2011

Reviewed by Robert Jasmer, MD; Associate Clinical Professor of Medicine, University of California, San Francisco.

Medical schools devoted a median of five hours of classroom time to teaching about the healthcare needs of lesbian, gay, bisexual, and transgender patients, a survey revealed.

A third of 132 schools in the U.S. and Canada that responded to the survey spent no time on the issues during the clinical part of medical training, according to Mitchell Lunn, MD, of Brigham and Women’s Hospital in Boston, and colleagues.

Nine schools (6.8%) reported they had no time devoted to such issues during preclinical years and five (3.8%) said such issues played no part of their curriculum, Lunn and colleagues reported in the Sept. 7 issue of the *Journal of The American Medical Association*.

Lesbian, gay, bisexual, and transgender people have a range of specific healthcare needs, including the risk of HIV and adolescent mental health, and are "more likely [than heterosexual patients] to face barriers accessing appropriate medical care," Lunn and colleagues argued.

The Association of American Medical Colleges has urged schools to educate medical students on those needs, but it’s not clear how well they are doing. To find out, Lunn and colleagues asked deans of medicine at all 141 allopathic medical schools in Canada and the U.S. and all 28 osteopathic schools in the U.S. to complete a 13-question Web-based questionnaire.

The questionnaire asked the deans to say how many hours were devoted to the issues; to state which of 16 topics specific to lesbian, gay, bisexual, and transgender patients were addressed; and to rate how well they thought their schools were doing.
All told, 150 schools responded, and 132 (or 75%) completed the questionnaire fully, Lunn and colleagues reported.

Analysis showed:
- The median number of curriculum hours devoted to the issues was five, with a range from 0 to 32, with a corresponding average value of seven.
- Most of those hours took place in the preclinical years, with a median of four hours versus two in the clinical years, a difference that was significant at $P<0.001$.
- Six of the 11 Canadian allopathic schools (54.5%) reported no clinical hours as did 12 of the 19 responding U.S. osteopathic schools (or 63.2%). In contrast, only 26 of the 102 U.S. allopathic schools (25.5%) said they had no clinical hours. The differences were significant at $P=0.001$.
- Most of the schools (128 or 97%) reported that they teach students to ask patients if they have sex with men, women, or both when obtaining a sexual history. And 95 (72%) reported teaching students the difference between sexual behavior and identity, while 28 schools (21.2%) did not know whether the difference was taught.
- 83 of the 132 schools (62.9%) reported teaching at least half of the 16 topics as part of the required curriculum and 11 (8.3%) said they taught all of them.
- Deans’ evaluation of their schools’ effort was most commonly "fair"—58 deans (43.9%) gave that response; 32 deans (24.2%) thought their curriculum was either "very good" or "good" and 34 (25.8%) thought it was either "very poor" or "poor," Lunn and colleagues reported.

The researchers cautioned that, despite a high response rate, the study might still not apply to all schools. As well, they noted, using reported classroom hours as a metric might underestimate the amount of time spent on issues relating to lesbian, gay, bisexual, and transgender patients. Some topics pertinent to this community might be covered in case studies, for instance.

The report is a "valuable snapshot" even if it likely misses some of the instructional time spent on those issues, according to Raymond Curry, MD, of the Northwestern University Feinberg School of Medicine in Chicago.

"That which is of most enduring importance is ... the assurance of ongoing attention to human sexuality, sexual behavior, and the accompanying medical implications as integral to the curriculum," he argued in an accompanying editorial.

Even if there were no healthcare disparities, Curry noted, "it would still be important for physicians to understand the full range of human sexual behavior and to address the related psychosocial as well as overtly medical needs of the patients in their care."


### California Legislature Passes Toni Atkins Bill on Preventative Medical Care for Youths

**San Diego Gay & Lesbian News**, (09.01.2011)

A bill to improve young people’s access to preventative STD care has advanced to Gov. Jerry Brown following passage by the state Legislature.

AB 499 would allow youths ages 12-17 to receive medical care to prevent infection with STDs. These services include vaccination against hepatitis B virus and human papillomavirus, the cause of most cases of cervical cancer, and post-exposure prophylaxis to prevent HIV infection.

“This bill will prevent adolescents from contracting life-threatening illnesses,” said Assembly member Toni Atkins (D-San Diego), the bill’s author. “It doesn’t make sense to leave out medical care to prevent STDs while allowing minors to access treatment after they’ve already been exposed.”

A California law on the books for more than 50 years permits youths ages 12-17 to consent to STD diagnosis and treatment; however, it makes no mention of preventative services, since these have been developed more recently.

Many other states—Alabama, Arkansas, Idaho, Iowa, Kansas, Maryland, Montana, North Carolina, South Carolina, South Dakota, and the District of Columbia—already have acted to close similar gaps in preventative services.

AB 499 was sponsored by the American Congress of Obstetricians and Gynecologists, the Health Officers Association of California, and the California STD Controllers Association.
Lack of Information Spreads Epidemics in North Korea

*Korea Times (Seoul)*, (09.04.2011)  Kim Tae-jong

Working in reclusive North Korea presents particular challenges to the Global Fund to Fight AIDS, TB and Malaria, according to a senior fund official.

“We don’t know much about AIDS in North Korea, and there are no official figures about AIDS in North Korea,” said Christoph Benn, the fund’s director of external relations. “One can suspect that there are also people who are infected with HIV in North Korea but there are no statistics, and also our UN partners don’t have concrete numbers about HIV in North Korea.”

Benn spoke while attending the 10th International Conference on AIDS in Asia and the Pacific, held in Busan, South Korea, Sept. 2-6. He noted the Global Fund is currently financing $32 million in TB and malaria programs in North Korea.

“We’ve already supported 1,500 tuberculosis patients in North Korea through this program,” Benn said. “And it only started last year but already there has been a decline of 50 percent in malaria mobility in North Korea. So these programs are very effective, and they are saving lives and they are implemented in a very efficient way.”

Ensuring efficacy means working with other international agencies such as UNICEF to develop accountability measures. “North Korea is a particular problem,” said Benn. “We have to make sure that the money does not directly go to the North Korean government.”

The Cost-Effectiveness of Symptom-Based Testing and Routine Screening for Acute HIV Infection in Men Who Have Sex with Men in the USA

*AIDS Vol. 25; No. 14: P. 1779-1787*, (09.10.2011)  Jessie L. Juusola; Margaret L. Brandeau; Elisa F. Long; Douglas K. Owens; Erand Bendavid

Testing for HIV when flu-like symptoms are evident may offer a cost-effective alternative for early detection of HIV infection in men who have sex with men (MSM), reported the authors of the current study.

“Acute HIV infection often causes influenza-like illness (ILI) and is associated with high infectivity,” wrote the researchers, who estimated the effectiveness and cost-effectiveness of strategies to identify and treat acute HIV infection among US MSM.

Designed as a dynamic model of HIV transmission and progression, the study evaluated three testing approaches:

* viral load testing for individuals with ILI;
* expanded screening with antibody testing; and
* expanded screening with antibody and viral load testing.

The researchers included treatment with antiretroviral therapy for persons indentified as acutely infected. The main study outcomes were new HIV infections, discounted quality-adjusted life years (QALYs) and costs, and incremental cost-effectiveness ratios.

“At the present rate of HIV antibody testing, we estimated that 538,000 new infections will occur among MSM over the next 20 years,” the authors wrote. They calculated that expanding antibody screening coverage to 90 percent of MSM annually would reduce new infections by 2.8 percent and cost $12,582 per QALY gained.

While more expensive than expanded antibody screening, symptom-based viral load testing with ILI is more effective, reducing new infections by 4.2 percent at a cost of $22,786 per QALY gained. Combining expanded antibody screening with symptom-based viral load testing reduced new infections by 5.7 percent at a cost of $29,923 per QALY gained. Adding viral load testing to all annual HIV antibody tests would further increase the detection rate, but at a prohibitively expensive cost of more than $100,000 per QALY gained.

“Targeted viral load testing of symptomatic MSM provides approximately 80 percent of the benefit of universal viral load testing at less than half the cost,” the authors wrote. “Use of HIV viral load testing in MSM with [ILI] prevents more infections than does annual antibody screening alone and is cost-effective.”

Bill Halting Local Circumcision Bans Goes to Brown

*Associated Press*, (09.06.2011)

Local jurisdictions would be prohibited from banning male circumcision under a bill passed by the state Legislature and sent to Gov. Jerry Brown on Tuesday. AB 768 was written by Assembly member Mike
Gatto (D-Los Angeles) in response to attempts by activists to ask San Francisco voters to ban the procedure on males under age 18. That proposed ballot measure has been blocked by a judge. Proponents of the operation say it can reduce the risk of STDs, HIV, and cancer, and they note its cultural importance to Jews and Muslims. Opponents say the surgery is unnecessary and can cause health problems.

**Sexual coercion common among students in Uganda**

Almost one third of students at a university in Uganda say that they have been subject to sexual coercion, an experience which was often linked to risky sexual behaviour. This is shown in a study from Lund University in Sweden. The study's findings could lead to a new approach in the work to combat HIV in Uganda.

The link between being subjected to sexual coercion and engaging in risky sexual behaviour by making an early sexual debut and having many sexual partners is significant in the work to prevent HIV, in the view of to Anette Agardh, the researcher who has led the study.

"African HIV campaigns are primarily aimed at young people who are sexually active. However, if the reasons for risky sexual behaviour are found to lie in experiences of sexual coercion, it is equally important to target those who commit such assaults. This doesn't have to be other young people; it is just as likely to be relatives, neighbours, teachers or other adults", she says.

It is not possible to discern time and causal relationships from the study, that is to say, we cannot know whether the sexual coercion preceded the behaviour of having many sexual partners. However, other studies have shown that such a pattern exists. "There are a number of studies which show that assaults also have a harmful effect on self-confidence", Dr Agardh adds. "Victims often have lower self-worth afterwards and tend to take less care of themselves, their integrity and their bodies."

Surprisingly, almost as many young men as young women said that they had been subject to sexual coercion – 29.9 per cent of men compared with 33.1 per cent of women. This was an unexpected result, because in Ugandan society there is high inequality between the sexes and strong opposition to homosexuality. Homosexual acts are illegal and are punishable with up to 14 years in prison. In the spring a bill to increase the sentence to the death penalty was shelved after strong international protests, but it still looms as a possibility.

"Previous international research on sexual coercion has primarily studied women, since it was believed that it is primarily girls and women who are affected. We did not expect to find such a high percentage among the young men in our study", says Dr Agardh.

The study took the form of a questionnaire distributed to all 1 220 undergraduate students at Mbarara University of Science and Technology in south-western Uganda 80 per cent of whom responded to the questionnaire. Sexual coercion was defined as "a sexual act which you have been forced to perform", with examples given including oral sex.

However, not all the young people who had been subject to sexual coercion displayed risky sexual behaviour. Factors which appeared to protect against this risky sexual behaviour were good mental health, a high level of trust in others and a family background in which religion played a major role. The researchers believe that these risk factors could also be taken into consideration in future efforts to combat HIV in Uganda.

**Nigeria: Cross River to Imprison HIV/Aids Victims If...**

Eyo Charles
8 September 2011

Calabar — People living with HIV/AIDS will be jailed for life if they wilfully transmit the virus to uninfected persons, according to a new law passed by the Cross River State House of Assembly and assented to by Governor Liyel Imoke.

The law known as the Cross River State Stigmatization and Discrimination Law No 9, of 2010, provides that any person or group that stigmatizes anyone living with HIV/AIDS in the state or intentionally infects another would be prosecuted. This was disclosed during a one-day awareness workshop organized by the Cross River State Agency for the Control of Aids (SACA) to sensitize journalists in the state on the existence of the new law.

According to Barrister Iko Ikoma of the state's Ministry of Justice, the new law which is in three parts, provides that any infected person who deliberately transfers the disease to another person would be charged to court and if found guilty, would be jailed for life.
Also speaking at the event, the Director General of SACA, Dr. Irene Aniyom said according to the new law, any false report against persons living with the disease by journalists and other organizations warrants severe sanction, ranging from N500,000.00 fine to life imprisonment or both. She added that the law is to give infected persons a sense of belonging.

The World Bank/SACA Project Manager, Mr. Gabe Undelikwo on his part said SACA would work out a plan to train journalists on the right terms to use when writing on HIV/AIDS issues.

Gay Men Could Soon Be Allowed to Donate Blood

_Edmonton Journal_, (09.09.2011)  Laura Baziuk, Postmedia News

Canada could be the next country to relax its absolute ban on blood donations from any man who has had sex with another man since 1977, a move that may gain momentum following the United Kingdom’s recent policy shift on MSM blood donors.

The United Kingdom on Thursday announced that health ministers in England, Scotland, and Wales will end a lifetime blood donation ban for MSM that began in the 1980s as a response to AIDS. From Nov. 7, these three UK countries will begin accepting as blood donors MSM who have been sexually abstinent for one year, among other criteria. They join Australia and Italy in retooling MSM blood donor eligibility policies.

“Certainly we already have a process underway where we’re looking to see about changing from a permanent to a time-based deferral,” said Dr. Dana Devine, Canadian Blood Services’ (CBS) vice president of medical, scientific and research affairs. “It is a step-wise thing and we have lots of consultation to do. I do think it will happen in Canada.”

CBS is working in partnership with the Canadian Institutes of Health Research; any policy change would have to be approved by Health Canada. CBS has previously cited the need for further research before relaxing the lifetime ban, but the experience of a tainted blood scandal in the 1980s also remains a barrier.

“People, I think appropriately, carry the recollection of that,” said Devine. “We’re not going to do anything that adds increased risk.”

“The challenge is making change palatable to various stakeholders, including Health Canada, the government, and the people of Canada,” said Doug Elliot, who represented the Canadian AIDS Society in investigating the government’s early response to HIV in the blood supply. “Unfortunately, I fear that it may take another crisis to do it,” such as fatalities from blood shortages, he said. “I hope it doesn’t get that far.”

Relationship Characteristics and Sexual Risk-Taking in Young Men Who Have Sex with Men

_Health Psychology Vol. 30; No. 5: P. 597-605_, (09..2011)  Brian Mustanski; Michael E. Newcomb; Elise M. Clerkin

Considering oneself to be in a serious relationship was associated with an eight-fold increase in the rate of unprotected sex in this study of young US MSM.

Epidemiological research, the authors wrote, “suggests that the majority of [HIV] transmissions among MSM are occurring in the context of primary partnerships, but little research has been done on the processes within these dyads that increase HIV risk behaviors.” The researchers used longitudinal partnership-level data to explore the effects of partner and relationship characteristics on the frequency of unprotected sex within young MSM relationships.

The participants, 122 MSM ages 16-20 at baseline, were assessed at three points, six months apart, with 91 percent retention at the 12-month follow-up wave. More than 80 percent of the MSM were racial/ethnic minorities. At each wave, the participants reported characteristics of their relationships and partners for up to three sex partners. Hierarchical linear modeling was used for analyses.

The largest effect was noted for considering one’s relationship to be serious, “which was associated with nearly an eight-fold increase in the rate of unprotected sex,” the authors found. Older partners, drug use before sex, physical violence, forced sex, and being in a relationship for more than six months also increased risk behaviors. Meeting partners online was not associated with significantly more sexual risk.

“These data provide insight into the relationship processes that should be addressed in prevention programs targeted at young MSM,” the authors concluded. “Relationships may serve as a promising unit for HIV prevention interventions, although more formative research will be required to address potential logistical obstacles to implementing such interventions. The partner-by-partner analytic approach (i.e.,
evaluating situational variables associated with several partners for a given participant) holds promise for future HIV behavioral research.”

**Candidate Malaria Vaccine Represents 'Potentially Encouraging Anti-Malaria Strategy,' Researchers Say**

A team of researchers led by Stephen Hoffman of Sanaria Inc. has created a candidate malaria vaccine against Plasmodium falciparum, the most deadly of the malaria parasites, using live but weakened parasites that "represents a potentially encouraging anti-malaria strategy," an NIH/National Institute of Allergy and Infectious Diseases press release reports. The findings of the research, which "was conducted by scientists at the Vaccine Research Center (VRC) of the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, working in concert with a large team of collaborators," were published in Thursday’s online issue of Science, the press release states (9/8).

"An effective malaria vaccine ... must prevent infection in greater than 80 percent of recipients for six to 24 months in order to be suitable for elimination campaigns and protecting travelers," but no such vaccine currently exists, according to a PR Newswire press release (9/8). "Sanaria's vaccine aims for 90 percent protection or even higher," says Hoffman, a former U.S. Navy researcher, who added, "Past results suggest that this target is possible," according to Science. "A new clinical trial in which the vaccine will be given intravenously to 51 volunteers is scheduled to start next month at VCR; another trial in Tanzania is on the drawing board," Science reports (Enserink, 9/8).

**Australian Scientists Create Iron-Rich 'Super Rice'**

Scientists from three universities in South Australia and the University of Melbourne have created genetically modified rice that "has up to four times more iron than conventional rice and twice as much zinc" in an effort to "provide a solution to the iron and zinc deficiency disorders that affect billions of people throughout the world," News Corp Australian Papers/Fox News reports. "Rice is the main food source for roughly half the world's population, including billions of people in developing countries across Asia, but the polished grain is too low in iron, zinc and Vitamin A to meet dietary needs," the news agency notes.

Scientists began field trials in the Philippines, but it will take several seasons "to determine if the rice is growing properly and consistently taking up sufficient iron and zinc" before it becomes available for human consumption, according to the the news agency (9/8).

**Haiti's Cholera Epidemic, The Hemisphere's Worst In Decades, Neglected By International Community**

"Cholera in Haiti is the worst epidemic that this hemisphere has seen in decades, yet it has received relatively little attention," Mark Weisbrot, co-director of the Center for Economic and Policy Research and president of Just Foreign Policy writes in this Al Jazeera opinion piece, adding, "The international community has failed Haiti in so many ways and for so many years that it is almost unimaginable."

"Perhaps if it were seen as the emergency, scandal, and outrage that it really is, international donors would be more willing to make the necessary investments in prevention and treatment," which is "ultimately the most effective way to reduce the toll of the disease and to eventually eliminate it," he writes. "But since the earthquake we have a situation in which U.S. residents have given $1.4 billion to private charities to help Haiti, and the U.S. government has appropriated $1.14 billion," he notes (9/8).

**Cumulative viral load: an important measure of risk of death in patients with HIV**

Michael Carter

Published: 12 September 2011

Cumulative viral load—the total amount of viral replication measured over a long period—is associated with the risk of death for patients with HIV, US research published in the online edition of Clinical Infectious Diseases shows.

The investigators calculated cumulative viral load, or “viremia copy years” for 2027 patients.

They explain: “10,000 copy-years of viremia is equal to having a VL [viral load] of 10,000 copies/ml for one year or a VL of 1000 copies/ml for ten years.”

After adjusting for potential confounders—including CD4 cell count—the investigators found that each log_{10} increase in viremia copy-years increased the risk of death by 44%.
“These findings substantiate growing recognition that HIV replication may cause or accelerate disease independent of its effect on...CD4 cell depletion,” comment the investigators.

Viral load is one of the key tests used to monitor patients with HIV and is an important research tool. However, reliance on single, “snap-shot” viral load results fails to measure a patient’s cumulative exposure to viral replication over time.

High levels of HIV replication are known to lower CD4 cell count. But there is also a growing realisation that uncontrolled HIV infection can cause irreparable damage to the immune system and organs. Moreover, the inflammatory effects of HIV replication may also contribute to the development of cardiovascular disease and some other illnesses not normally associated with HIV.

Investigators from the US Centers for AIDS Research Network of Integrated Clinical Systems speculated that there would be a strong relationship between cumulative viral load, or viremia copy-years and the risk of death for patients with HIV.

They therefore monitored patients who started HIV therapy for the first time between 2000 and 2008.

At baseline, median CD4 cell count was 222 cells/mm$^3$ and median viral load was $4.8 \log_{10}$ copies/ml (63,000 copies/ml).

Patients were followed for a median of 2.7 years and contributed a total of 6579 person-years of follow-up.

Each patient had a median of eight viral load tests, and the total number of viral load measurements was 21,665.

Treatment outcomes were excellent. After 24 weeks, 81% of patients had an undetectable viral load, and during the total period of follow-up 82% of viral load measurements were below the limit of detection.

Over the course of the study, the median viremia copy-years was $5.3 \log_{10}$ (199,500) copies x years/ml. A total of 85 patients (4%) died, a mortality rate of 1.3 per 100 person years. The median time to death was two years.

The investigators’ first set of analysis showed that each one log$_{10}$ viremia copy x years increased the risk of death was 81% (HR = 1.81; 95% CI, 1.51-2.18; p < 0.001). Mortality risk was also associated with viral load after 24 weeks of treatment (p < 0.001) and most recent viral load (p < 0.001).

A statistical model that included the patients’ demographic and clinical details as well as their baseline, 24-week and most recent viral load was then designed.

This showed that each one log$_{10}$ viremia copy x years increased the risk of death by 44% (HR = 1.44; 95% CI, 1.07-1.94; p = 0.02).

“Viremia copy years, a measure of cumulative plasma HIV RNA exposure...demonstrated a strong association with all-cause mortality in a large sample of HIV-infected patients who started ART,” write the authors.

“We suggest that viremia copy-years play an important and complementary role to cross-sectional VL measures and transform the role of VL in future...research initiatives as well as in clinical care.”

Each ten-year increase in age was associated with a 51% increase in mortality risk (HR = 1.51; 95% CI, 1.18-1.94; p = 0.001). However, each 100 cell/mm$^3$ increase in CD4 cell count significantly reduced the risk of death (p < 0.001).

The investigators believe that cumulative viral exposure is a “surrogate for and perhaps the underlying driver of cumulative inflammation and immune system activation,” leading to an increased risk of inflammation-related diseases for patients with uncontrolled viral load.

Because of the ageing of the HIV-infected population and therefore their increased risk of inflammation-related diseases, the investigators believe that “cumulative measures of HIV burden may take on increased importance in the coming years.”

However, they admit that their study has limitations, highlighting both its cross-sectional design and relatively short follow-up period. Moreover, they did not have sufficient information on causes of death to evaluate the relationship between viremia copy-years with AIDS and non-AIDS-related deaths.

“Future research should evaluate the relationship between viremia copy-years and biomarkers of inflammation and immune system activation longitudinally, as well as the value of this measure in predicting AIDS and non-AIDS clinical events, and in modelling the HIV transmission risk over time.”

Reference

India probes child HIV cases after blood transfusions

An investigation has been launched into how 23 children who received regular blood transfusions have tested positive for HIV in the Indian state of Gujarat.

The children suffer from thalassaemia and get their blood transfusions at a public hospital in Junagadh district.

Hospital authorities have denied that the children were infected by their blood supplies.

But state authorities have launched a probe after routine tests of nearly 100 children revealed the latest cases.

About 2.5m people in India have the HIV virus, according to UN-backed government figures. Gujarat, along with Bihar and Uttar Pradesh, account for 22% of HIV infections in India.

The 23 infected children in the latest case are aged between five and 10 years.

They showed positive for HIV following recent tests of nearly 100 children suffering from thalassaemia and who receive blood transfusions at the hospital twice a week.

Gujarat Health Minister Jay Narayan Vyas said that the children may have been infected after receiving transfusions "at some other places".

He also said some pre-transfusion tests at the hospital had found that the children already had HIV.

But the parents of the infected children insist that they only ever got transfusions at the Junagadh government hospital.

"We have never gone anywhere else [for blood transfusions]. How can they (authorities) say that children were affected with the virus before getting registered?," Salim Sheikh, the father of one child, told The Indian Express newspaper.

Indian authorities say the number of annual new HIV infections has declined by more than 50% during the last decade.

Mistaken Assumptions and Missed Opportunities: Correlates of Undiagnosed HIV Infection Among Black and Latino Men Who Have Sex with Men

Journal of Acquired Immune Deficiency Syndromes Vol. 58; No. 1: P. 64-71, (09.01.2011) Gregorio A. Millett, MPH; Helen Ding, MD, MS, MSPH; Gary Marks PhD; William L. Jeffries IV, PhD, MPH; Trista Bingham, MPH, PhD; Jennifer Lauby, PhD; Christopher Murrill, PhD, MPH; Stephen Flores, PhD; Ann Steuve, PhD, MPH

The authors of the current study sought to identify the correlates of being HIV-positive but unaware among black and Latino men who have sex with men. These men were compared with HIV-negative MSM in bivariate and multivariate analyses.

Participants in three cities completed a computer-assisted interview and were tested for HIV. Of 1,208 MSM (597 black; 611 Latino) tested, 11 percent were unaware they were HIV-positive (18 percent black; 5 percent Latino).

Multivariate analysis showed being Latino HIV-positive unaware was associated with non-gay identity, high perceived risk of being HIV-positive, and belief that sex with other Latino MSM reduces HIV risk. Among black MSM, being HIV-positive unaware was associated with gay identity, moderately higher income, having health insurance, disclosure of sexuality to health care provider, fewer than three lifetime HIV tests, high perceived risk of being HIV-positive, and belief that sex with other black MSM reduces HIV risk.

"HIV prevention efforts should address misperceptions among those black and Latino MSM who believe assortative (i.e., intra-racial) sexual mixing reduces risk of HIV infection," the authors suggested. "Our findings also revealed missed opportunities to diagnose black MSM with HIV infection who were already engaged in care and had disclosed their sexuality to their health care provider. Clinicians should offer HIV testing to all MSM, particularly black MSM who disclose engaging in recent sex with other men, to facilitate earlier diagnosis of HIV infection and reduce transmission risk to sexual partners."
HIV Vaccine Development — Improving on Natural Immunity
Margaret I. Johnston, Ph.D., and Anthony S. Fauci, M.D.

Although a number of methods of preventing infection with the human immunodeficiency virus (HIV) have proven effective to varying degrees, it is generally agreed that a safe and effective vaccine against HIV infection would be a critical component of a highly effective prevention toolkit for controlling and ultimately ending the global AIDS pandemic. For nearly all important pathogens for which effective vaccines have been developed, such as smallpox, measles, and poliovirus, there exists a natural model of protection: the immune response to the pathogen ultimately clears the microbe from the body and confers durable protection against reinfection. Under these circumstances, the human immune system has already provided us with proof of the concept that it can generate a protective response. This fact has led to a fundamental tenet of vaccinology: the best way to develop an effective vaccine is to design a candidate that mimics infection and induces responses akin to natural immunity.

Unfortunately, this lesson does not apply to HIV infection. We have known since the mid-1980s that the body’s natural immune response to HIV infection is completely inadequate. A “natural” immune response that might adequately control HIV infection does not occur at all, occurs too rarely, is too weak, or is too slow to begin. Thus, a key goal for an effective HIV vaccine is to induce in the recipient a response that differs qualitatively, quantitatively, or both from that induced by natural infection — a response that has been referred to as “unnatural immunity.”

Although an HIV-vaccine candidate was recently shown to be modestly protective, it induced neither broadly neutralizing antiserum nor broadly reactive cytotoxic T-cell responses against HIV. This finding raises the possibility that a modest degree of protection against HIV acquisition could be mediated by non-neutralizing mechanisms — for example, antibody-dependent cell-mediated cytotoxicity, antibody-dependent cell-mediated viral inhibition, or other responses not classically associated with vaccine efficacy. Nonetheless, with most viral infections, the appearance of antibodies, particularly neutralizing antibodies, correlates closely with clearance of the virus and subsequent protection from reinfection. Thus, induction of neutralizing antibodies has served as the gold standard for vaccine-induced protection against infection — and is an appropriate goal for HIV infection as well, given that passive infusion of several broadly neutralizing antibodies completely prevented virus acquisition in nonhuman primate models of AIDS. Although non-neutralizing antibody functions appeared to contribute somewhat to protection in this model, and although conserved regions of internal proteins could serve as important vaccine targets, an HIV vaccine that results in the production of broadly neutralizing antibodies before or very soon after exposure to HIV is likely to be highly effective. Since HIV infection does not naturally induce broadly neutralizing antibodies, a key challenge is inducing such antibodies.

Neutralizing antibodies generated during HIV infection are mostly directed toward exposed, highly variable portions of the HIV envelope protein on the viral particle. Antibodies found early in the course of HIV infection are directed at the infecting viral strain, which rapidly evolves to escape recognition. In contrast, antibodies that neutralize a broad array of HIV strains — broadly neutralizing antibodies — are directed against highly conserved regions of the envelope that are essential for viral entry into the host cell. Unfortunately, these conserved sites are recessed, hidden by glycans, partially embedded in the viral membrane, or otherwise relatively inaccessible to recognition by the immune system. For these reasons, broadly neutralizing antibodies are rarely found in the serum of acutely infected persons. When they do appear, they are detected at least 1 to 2 years after initial infection and do not seem to be clinically relevant.

An important challenge for HIV vaccinologists is to design vaccines that induce these unnatural immune responses. The application of new research tools to the study of broadly neutralizing antibodies is helping to guide the design of vaccines that might induce such antibodies. Until recently, the body was thought to be incapable of producing these antibodies; only a few monoclonal antibodies that were broadly neutralizing had been found, and rarely were they derived from the B cells of HIV-infected patients. However, with the utilization of extremely-high-throughput screening of B-cell clones derived from HIV-infected persons, the rapid cloning of their immunoglobulin genes, and characterization of the resulting monoclonal antibodies, it became clear that many patients can indeed make broadly neutralizing antibodies. Unfortunately, they do so only after the establishment of persistent infection. In this regard, the ability to screen tens of millions of B-cell clones for HIV-envelope specificity has allowed researchers to isolate additional broadly neutralizing monoclonal antibodies and precisely identify their target...
epitopes on the HIV envelope (see figure HIV-1 Epitopes Targeted by Broadly Neutralizing Human Monoclonal Antibodies.).

A recent research focus has been on “structure-based vaccine design” — that is, applying knowledge of the crystallographic structure and conformation of the HIV-envelope epitope in the context of the binding site of a broadly neutralizing monoclonal antibody to design a vaccine that effectively presents that epitope in its relevant conformation to the immune system. Crystallographic studies have revealed that broadly neutralizing and non-neutralizing antibodies can bind to the same conserved region of the envelope in similar but subtly different ways. Thus, determining how to replicate the precise three-dimensional conformation of the HIV-envelope epitope as it resides in the antibody binding site will prove challenging. One approach being actively pursued is scaffolding the desired epitope onto an exposed portion of a soluble or membrane-associated protein.

However, producing an antibody with high avidity to the highly conserved regions of the HIV envelope may prove to be more complex than simply presenting the desired envelope epitope to the immune system. All potent broadly neutralizing antibodies that have been described to date have one or more unusual structural features that may result only from years of chronic viral infection and exposure to viral antigen. These structural features appear to arise through a complex evolutionary process, referred to as “somatic hypermutation,” which over time generates B cells that produce antibodies of increasingly higher avidity. Whether a B cell must undergo a long evolutionary process to produce a broadly neutralizing antibody against HIV remains uncertain. If such a process were required, that would pose a sobering challenge to HIV vaccinologists. Researchers are now dissecting the steps in this evolutionary process to understand how B cells evolve for the production of broadly neutralizing HIV antibodies and to design novel vaccines that might accelerate that process.

Thus, we have learned that the body is indeed capable of producing potent, broadly neutralizing antibodies; however, it does not do so readily or efficiently. We are optimistic that the tools of modern science will enable us to develop HIV vaccines that induce effective immune responses that do better than natural immunity and prevent HIV infection.

September 12, 2011

An Immune System Trained to Kill Cancer ****

By Denise Grady

PHILADELPHIA — A year ago, when chemotherapy stopped working against his leukemia, William Ludwig signed up to be the first patient treated in a bold experiment at the University of Pennsylvania. Mr. Ludwig, then 65, a retired corrections officer from Bridgeton, N.J., felt his life draining away and thought he had nothing to lose.

Doctors removed a billion of his T-cells — a type of white blood cell that fights viruses and tumors — and gave them new genes that would program the cells to attack his cancer. Then the altered cells were dripped back into Mr. Ludwig’s veins.

At first, nothing happened. But after 10 days, hell broke loose in his hospital room. He began shaking with chills. His temperature shot up. His blood pressure shot down. He became so ill that doctors moved him into intensive care and warned that he might die. His family gathered at the hospital, fearing the worst.

A few weeks later, the fevers were gone. And so was the leukemia.

There was no trace of it anywhere — no leukemic cells in his blood or bone marrow, no more bulging lymph nodes on his CT scan. His doctors calculated that the treatment had killed off two pounds of cancer cells.

A year later, Mr. Ludwig is still in complete remission. Before, there were days when he could barely get out of bed; now, he plays golf and does yard work.

“I have my life back,” he said.
Mr. Ludwig's doctors have not claimed that he is cured — it is too soon to tell — nor have they declared victory over leukemia on the basis of this experiment, which involved only three patients. The research, they say, has far to go; the treatment is still experimental, not available outside of studies.

But scientists say the treatment that helped Mr. Ludwig, described recently in The New England Journal of Medicine and Science Translational Medicine, may signify a turning point in the long struggle to develop effective gene therapies against cancer. And not just for leukemia patients: other cancers may also be vulnerable to this novel approach — which employs a disabled form of H.I.V.-1, the virus that causes AIDS, to carry cancer-fighting genes into the patients' T-cells. In essence, the team is using gene therapy to accomplish something that researchers have hoped to do for decades: train a person's own immune system to kill cancer cells.

Two other patients have undergone the experimental treatment. One had a partial remission: his disease lessened but did not go away completely. Another had a complete remission. All three had had advanced chronic lymphocytic leukemia and had run out of chemotherapy options. Usually, the only hope for a remission in such cases is a bone-marrow transplant, but these patients were not candidates for it.

Dr. Carl June, who led the research and directs translational medicine in the Abramson Cancer Center at the University of Pennsylvania, said that the results stunned even him and his colleagues, Dr. David L. Porter, Bruce Levine and Michael Kalos. They had hoped to see some benefit but had not dared dream of complete, prolonged remissions. Indeed, when Mr. Ludwig began running fevers, the doctors did not realize at first that it was a sign that his T-cells were engaged in a furious battle with his cancer. Other experts in the field said the results were a major advance.

“It's great work,” said Dr. Walter J. Urba of the Providence Cancer Center and Earle A. Chiles Research Institute in Portland, Ore. He called the patients' recoveries remarkable, exciting and significant. “I feel very positive about this new technology. Conceptually, it's very, very big.”

Dr. Urba said he thought the approach would ultimately be used against other types of cancer as well as leukemia and lymphoma. But he cautioned, “For patients today, we're not there yet.” And he added the usual scientific caveat: To be considered valid, the results must be repeated in more patients, and by other research teams.

Dr. June called the techniques “a harvest of the information from the molecular biology revolution over the past two decades.”

**Hitting a Genetic Jackpot**

To make T-cells search out and destroy cancer, researchers must equip them to do several tasks: recognize the cancer, attack it, multiply, and live on inside the patient. A number of research groups have been trying to do this, but the T-cells they engineered could not accomplish all the tasks. As a result, the cells' ability to fight tumors has generally been temporary.

The University of Pennsylvania team seems to have hit all the targets at once. Inside the patients, the T-cells modified by the researchers multiplied to 1,000 to 10,000 times the number infused, wiped out the cancer and then gradually diminished, leaving a population of “memory” cells that can quickly proliferate again if needed.

The researchers said they were not sure which parts of their strategy made it work — special cell-culturing techniques, the use of H.I.V.-1 to carry new genes into the T-cells, or the particular pieces of DNA that they selected to reprogram the T-cells.

The concept of doctoring T-cells genetically was first developed in the 1980s by Dr. Zelig Eshhar at the Weizmann Institute of Science in Rehovot, Israel. It involves adding gene sequences from different sources to enable the T-cells to produce what researchers call chimeric antigen receptors, or CARs — protein complexes that transform the cells into, in Dr. June's words, “serial killers.”

Mr. Ludwig's disease, chronic lymphocytic leukemia is a cancer of B-cells, the part of the immune system that normally produces antibodies to fight infection. All B-cells, whether healthy or leukemic, have on their surfaces a protein called CD19. To treat patients with the disease, the researchers hoped to reprogram their T-cells to find CD19 and attack B-cells carrying it.

But which gene sequences should be used to reprogram the T-cells, from which sources? And how do you insert them?

Various research groups have used different methods. Viruses are often used as carriers (or vectors) to insert DNA into other cells because that kind of genetic sabotage is exactly what viruses normally specialize in doing. To modify their patients' T-cells, Dr. June and his colleagues tried a daring approach: they used a disabled form of H.I.V.-1. They are the first ever to use H.I.V.-1 as the vector in gene therapy for cancer patients (the virus has been used in other diseases).
The AIDS virus is a natural for this kind of treatment, Dr. June said, because it evolved to invade T-cells. The idea of putting any form of the AIDS virus into people sounds a bit frightening, he acknowledged, but the virus used by his team was “gutted” and was no longer harmful. Other researchers had altered and disabled the virus by adding DNA from humans, mice and cows, and from a virus that infects woodchucks and another that infects cows. Each bit was chosen for a particular trait, all pieced together into a vector that Dr. June called a “Rube Goldberg-like solution” and “truly a zoo.”

“It incorporates the ability of H.I.V. to infect cells but not to reproduce itself,” he said.

To administer the treatment, the researchers collected as many of the patients’ T-cells as they could by passing their blood through a machine that removed the cells and returned the other blood components back into the patients’ veins. The T-cells were exposed to the vector, which transformed them genetically, and then were frozen. Meanwhile, the patients were given chemotherapy to deplete any remaining T-cells, because the native T-cells might impede the growth of the altered ones. Finally, the T-cells were infused back into the patients.

Then, Dr. June said, “The patient becomes a bioreactor” as the T-cells proliferate, pouring out chemicals called cytokines that cause fever, chills, fatigue and other flulike symptoms.

The treatment wiped out all of the patients’ B-cells, both healthy ones and leukemic ones, and will continue to do for as long as the new T-cells persist in the body, which could be forever (and ideally should be, to keep the leukemia at bay). The lack of B-cells means that the patients may be left vulnerable to infection, and they will need periodic infusions of a substance called intravenous immune globulin to protect them.

So far, the lack of B-cells has not caused problems for Mr. Ludwig. He receives the infusions every few months. He had been receiving them even before the experimental treatment because the leukemia had already knocked out his healthy B-cells.

One thing that is not clear is why Patient 1 and Patient 3 had complete remissions, and Patient 2 did not. The researchers said that when Patient 2 developed chills and fever, he was treated with steroids at another hospital, and the drugs may have halted the T-cells’ activity. But they cannot be sure. It may also be that his disease was too severe.

The researchers wrote an entire scientific article about Patient 3, which was published in The New England Journal of Medicine. Like the other patients, he also ran fevers and felt ill, but the reaction took longer to set in, and he also developed kidney and liver trouble—a sign of tumor lysis syndrome, a condition that occurs when large numbers of cancer cells die off and dump their contents, which can clog the kidneys. He was given drugs to prevent kidney damage. He had a complete remission.

What the journal article did not mention was that Patient 3 was almost not treated.

Because of his illness and some production problems, the researchers said, they could not produce anywhere near as many altered T-cells for him as they had for the other two patients—only 14 million (“a mouse dose,” Dr. Porter said), versus 1 billion for Mr. Ludwig and 580 million for Patient 2. After debate, they decided to treat him anyway.

Patient 3 declined to be interviewed, but he wrote anonymously about his experience for the University of Pennsylvania Web site. When he developed chills and a fever, he said, “I was sure the war was on—I was sure C.L.L. cells were dying.”

He wrote that he was a scientist, and that when he was young had dreamed of someday making a discovery that would benefit mankind. But, he concluded, “I never imagined I would be part of the experiment.”

When he told Patient 3 that he was remission, Dr. Porter said, they both had tears in their eyes.

**Not Without Danger to Patients**

While promising, the new techniques developed by the University of Pennsylvania researchers are not without danger to patients. Engineered T-cells have attacked healthy tissue in patients at other centers. Such a reaction killed a 39-year-old woman with advanced colon cancer in a study at the National Cancer Institute, researchers there reported last year in the journal Molecular Therapy.

She developed severe breathing trouble 15 minutes after receiving the T-cells, had to be put on a ventilator and died a few days later. Apparently, a protein target on the cancer cells was also present in her lungs, and the T-cells homed in on it.

Researchers at Memorial Sloan Kettering Cancer in New York also reported a death last year in a T-cell trial for leukemia (also published in Molecular Therapy). An autopsy found that the patient had apparently died from sepsis, not from the T-cells, but because he died just four days after the infusion, the researchers said they considered the treatment a possible factor.
Dr. June said his team hopes to use T-cells against solid tumors, including some that are very hard to treat, like mesothelioma and ovarian and pancreatic cancer. But possible adverse reactions are a real concern, he said, noting that one of the protein targets on the tumor cells is also found on membranes that line the chest and abdomen. T-cell attacks could cause serious inflammation in those membranes and mimic lupus, a serious autoimmune disease.

Even if the T-cells do not hit innocent targets, there are still risks. Proteins they release could cause a "cytokine storm"—high fevers, swelling, inflammation and dangerously low blood pressure — which can be fatal. Or, if the treatment rapidly kills billions of cancer cells, the debris can damage the kidney and cause other problems.

Even if the new T-cell treatment proves to work, the drug industry will be needed to mass produce it. But Dr. June said the research is being done only at universities, not at drug companies. For the drug industry to take interest, he said, there will have to be overwhelming proof that the treatment is far better than existing ones.

"Then I think they'll jump into it," he said. "My challenge now is to do this in a larger set of patients with randomization, and to show that we have the same effects."

Mr. Ludwig said that when entered the trial, he had no options left. Indeed, Dr. June said that Mr. Ludwig was "almost dead" from the leukemia, and the effort to treat him was a "Hail Mary."

Mr. Ludwig said: "I don't recall anybody saying there was going to be a remission. I don't think they were dreaming to that extent."

The trial was a Phase 1 study, meaning that its main goal was to find out whether the treatment was safe, and at what dose. Of course, doctors and patients always hope that there will be some benefit, but that was not an official endpoint.

Mr. Ludwig thought that if the trial could buy him six months or a year, it would be worth the gamble. But even if the study did not help him, he felt it would still be worthwhile if he could help the study.

When the fevers hit, he had no idea that might be a good sign. Instead, he assumed the treatment was not working. But a few weeks later, he said that his oncologist, Dr. Alison Loren, told him, "We can't find any cancer in your bone marrow."

Remembering the moment, Mr. Ludwig paused and said, "I got goose bumps just telling you those words."

"I feel wonderful," Mr. Ludwig said during a recent interview. "I walked 18 holes on the golf course this morning."

Before the study, he was weak, suffered repeated bouts of pneumonia and was wasting away. Now, he is full of energy. He has gained 40 pounds. He and his wife bought an R.V., in which they travel with their grandson and nephew. "I feel normal, like I did 10 years before I was diagnosed," Mr. Ludwig said. "This clinical trial saved my life."

Dr. Loren said in an interview, "I hate to say it in that dramatic way, but I do think it saved his life."

Mr. Ludwig said that Dr. Loren told him and his wife something he considered profound. "She said, 'We don't know how long it's going to last. Enjoy every day,'" Mr. Ludwig recalled. "That's what we've done ever since."

Thinking of Getting Inked? Get Risks First
Desert Sun (Palm Springs), (09.08.2011)  Dr. Andrew Ordon

"Getting 'inked' has become increasingly common, especially with young people. Once reserved for bikers and sailors, this form of self-expression has risen in popularity in the last decade. ..."

"But are there health concerns to getting tattoos? The answer is a resounding 'Yes!'"

"Hepatitis C is a major concern for anyone having his or her skin broken by another person. ... It can be spread through blood contact, sharing a needle, and unprotected sex. ..."

"One study showed that people with tattoos are nine times more likely to have hepatitis C. But what does that mean? Did they get it from the tattoo or are people who have tattoos simply more likely to engage in activity that results in contracting the disease?"

"According to [CDC], you are more likely to get hepatitis C from your dentist than a proper tattoo artist. There are also no documented cases of someone getting HIV from a licensed tattoo artist, either."

"But that doesn't mean tattoos don't sometimes end in regret. Tattoo removal or alteration is a big business, indicating that remorse is common."

"Tattoo ink has also been shown to contain a low level of carcinogens, which cause cancer. That being said, no study has shown a direct link between skin cancer and tattoos."
“As doctors, we consider factors such as morbidity and cost in risk analysis of medical procedures. Tattoos carry both.

“There is no way to measure the satisfaction a person gets from being ‘inked’ — or the regret of having a tattoo you no longer want. Like so many things, it comes down to personal choice.”

The author is a Rancho Mirage-based plastic surgeon who can be seen on the syndicated TV show “The Doctors.”

**Hepatitis B and C Coinfection among HIV Positive People in the U.S.**

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Written by Liz Highleyman
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Liver disease and coinfection with hepatitis B or C are common among people with HIV, according to a recent analysis, leading researchers to recommend that viral hepatitis screening, vaccination, and treatment should be considered a priority for HIV positive individuals.

Since the advent of effective antiretroviral therapy (ART), liver disease—often related to hepatitis B virus (HBV) or hepatitis C virus (HCV) coinfection—has become a leading cause of illness and death among people with HIV.

As described in the April 14, 2011, *World Journal of Gastroenterology*, Susan Buskin from the Seattle and King County Department of Public Health and colleagues evaluated trends and risk factors for liver disease and viral hepatitis among HIV positive people age 13 and older.

The analysis included 29,490 participants in the Adult/Adolescent Spectrum of HIV-related Diseases Project, a multicenter review sponsored by the Centers for Disease Control and Prevention (CDC) that looked at medical records of HIV patients at more than 100 medical facilities in Atlanta, Dallas, Denver, Detroit, Houston, Los Angeles, New Orleans, New York City, Puerto Rico, San Antonio, and Seattle.

The project started collecting information in 1990, but the present analysis was restricted to data obtained between 1998 and 2004 (not long after the widespread adoption of combination ART). Every 6 months researchers collected data about presentation, treatment, and outcomes of HIV disease and associated conditions, including presence of liver disease, hepatitis screening, and hepatitis diagnosis. Participants were followed for 2.4 years on average, contributing a total 69,487 person-years of observation.

**Results**

- Overall, 3% of cohort participants were diagnosed with liver disease, 8% with chronic hepatitis B, and 19% with hepatitis C; 2% had both hepatitis B and C.
- 25% had a liver disease diagnosis at baseline (first record examined), while 75% developed new liver disease during follow-up.
- The rate of chronic hepatitis B diagnosis showed a small but significant rise, from 7% in 1998 to 9% in 2004.
- The rate of hepatitis C diagnosis nearly tripled over the same period, from 9% to 24%.
- 832 participants diagnosed with liver disease had the following conditions:
  - 31% with non-alcoholic cirrhosis (or alcohol not specified as a cause);
  - 20% with alcoholic cirrhosis;
  - 3% with a primary liver cancer;
  - 3% with liver failure not otherwise specified;
  - 29% with other liver disease.
- Over the course of follow-up, the rate of new or incident liver disease was 0.9 cases per 100 person-years.
- The incidence of chronic hepatitis B was 1.8 per 100 person-years, and the rate for hepatitis C was 4.7 per 100 person-years.
- Significant risk factors for new chronic hepatitis B diagnosis included male sex, men having sex with men, lower nadir (lowest-ever) CD4 T-cell count, injection drug use, alcohol use, and triple infection with HCV.
- Significant risk factors for new hepatitis C diagnosis included male sex, older age, white or Latino race/ethnicity, triple infection with HBV, injection drug use (4.7-fold higher risk), and hemophilia (7-fold higher).

In a multivariate analysis, independent predictors of liver disease included:
Older age, history of injection drug users, heavy alcohol consumption, and diagnosis of AIDS (CD4 T-cell count < 200 cells/mm³) was associated with greater risk.

Black patients had a lower rate than other racial/ethnic groups.

Neither ART use overall nor use of specific antiretroviral drugs was positively or negatively associated with liver disease after controlling for other factors including HBV and HCV.

- 25 participants were diagnosed with liver cancer, including 15 with hepatocellular carcinoma; 2 of these patients were lost to follow-up and the rest died.
- 13 patients with liver cancer had HCV and 10 had chronic HBV (including 2 people with both).

Mortality was much higher among people diagnosed with liver disease, 57% compared with 15% for the study population overall.

10% of all deaths occurred among participants with liver disease.

An estimated 1% of all deaths may have had liver disease as a cause or contributing factor, rising to 2% among people with HBV or HCV.

The likelihood of HBV and HCV screening increased significantly during the study period—from less than 20% to more than 60%—but repeat screening was uncommon, even for people with ongoing risk of infection.

Less than one-third of people without prior hepatitis B had a record of HBV vaccination, although this increased from 10% to 28% during the study period.

The researchers noted that despite care guidelines calling for HBV vaccination and hepatitis B and C screening for people with HIV, these were not universally performed (or if done, were not documented).

Based on these findings, they concluded, "Due to high rates of incident liver disease, viral hepatitis screening, vaccination, and treatment among HIV-infected individuals should be a priority."

"Although HBV vaccination rates have improved and screening rates for HBV and HCV have climbed steadily, they are still inadequate, and efforts are needed to improve vaccination and screening rates," they elaborated in their discussion.

"The high rates of incident HCV (5/100 person-years) indicate that individuals at risk should be screened and while remaining at risk, re-screened on a regular basis. Similarly, a sizable HBV incidence (2/100 person-years) supports improved screening and vaccination," they continued.

"Until better data are available, annual screenings for HCV and HBV vaccination discussions are suggested," they recommended. "Treatment of HBV and HCV should be considered for all HIV co-infected individuals.”

Reference

Two HPV Vaccine Doses May Protect as Well as Three
Published on Monday, 12 September 2011 00:00
Written by Liz Highleyman
HPV © Russell Kightley
The bivalent Cervarix human papillomavirus (HPV) vaccine may protect against cervical cancer with 2 doses, which would reduce inconvenience and cost compared with the current standard 3-dose regimen, according to study findings described in the September 9, 2011, advance online edition of the Journal of the National Cancer Institute.

Aimée Kreimer from the National Cancer Institute and colleagues assessed the effectiveness of 1 or 2 doses of Cervarix—which protects against high-risk (cancer-causing) HPV types 16 and 18—in the Costa Rica Vaccine Trial. The main study was designed to compare 3 doses of Cervarix versus control (a hepatitis A vaccine) in more than 7000 young women.

This sub-analysis looked at 802 women who received 2 doses and 384 participants who received only 1 dose, comparing them to 5967 women who received all 3 doses as intended, over a median follow-up period of about 4 years.
Results

- The rate of new or incident HPV type 16 or 18 infections persisting for at least 1 year was unrelated to number of vaccine doses.
- The number of HPV 16 or 18 infections was lower in the Cervarix arm compared with the placebo arm at all dose levels:
  - 3 doses: 25 and 133 new infections, respectively;
  - 2 doses: 3 and 17, respectively;
  - 1 dose: 0 and 10, respectively.
- Based on these numbers, vaccine efficacy was calculated to 80.9% for 3 doses, 84.1% for 2 doses, and 100% for 1 dose.

These results led the researchers to conclude, "Four years after vaccination of women who appeared to be uninfected, this nonrandomized analysis suggests that two doses of the HPV16/18 vaccine, and maybe even one dose, are as protective as three doses."

Below is an edited excerpt from a recent National Institutes of Health press release describing the study and its findings in more detail.

NIH Study Finds Two Doses of HPV Vaccine May Be as Protective as Full Course

September 9, 2011—Two doses of the human papillomavirus (HPV) vaccine Cervarix were as effective as the current standard three-dose regimen after four years of follow-up, according to researchers from the National Cancer Institute (NCI), part of the National Institutes of Health, and their colleagues. The results of the study, based on data from a community-based clinical trial of Cervarix in Costa Rica, appeared online Sept. 9, 2011, in the Journal of the National Cancer Institute.

Worldwide, approximately 500,000 new cases of cervical cancer are diagnosed every year, and about 250,000 women die from the disease. An overwhelming majority of these new cases and deaths occur in low-resource countries. Virtually all cases of cervical cancer are caused by persistent infection with HPV.

Cervarix is one of two vaccines approved by the U.S. Food and Drug Administration to protect against persistent infection with two carcinogenic HPV types, 16 and 18, which together account for 70 percent of all cervical cancer cases. The vaccine is intended to be administered in three doses given over the course of six months. To date, investigators have observed up to eight years of protection from persistent HPV infection with the vaccine. Studies are ongoing to determine the maximum length of protection.

The cost of the vaccine as well as the logistical difficulties of administering three doses to an adolescent population in resource-poor countries is greater than administering two doses. Even in wealthier countries such as the United States, few adolescent females complete the entire course of three vaccinations. According the Centers for Disease Control and Prevention, although approximately 49 percent of American girls ages 13 to 17 received one dose of the vaccine in 2010, only 32 percent received all three doses. In the United States, the predominately used HPV vaccine is Gardasil, which has a different formulation than Cervarix. Gardasil also protects against up to 90 percent of genital warts because it targets HPV strains 6 and 11 as well as 16 and 18.

The NCI-sponsored Costa Rica Vaccine Trial was designed to assess the efficacy of Cervarix in a community-based setting. Women ages 18 to 25 years were randomly assigned to receive the HPV vaccine or a Hepatitis A vaccine as the control treatment. Although the investigators intended to administer all three doses of the assigned vaccine to all 7,466 women in the study, about 20 percent of the participants received only one or two doses of the HPV or control vaccine. A third of women did not complete the vaccine series because they became pregnant or were found to have possible cervical abnormalities, reasons that would not likely bias the findings.

The investigators found that, after four years of follow up, two doses of the vaccine conferred the same strong protection against persistent infection with HPV 16 and 18 as did the full three-dose regimen. From just a single dose, they also observed a high level of protection, but they are cautious about the long-term efficacy of a single dose because other vaccines of this type usually require a booster dose. Additional studies are needed to evaluate the efficacy of a single dose, as well as the duration of protection for both one and two doses.

"Our study provides evidence that an HPV vaccine program using two doses will work. It may be that vaccinating more women, with fewer doses for each, will reduce cervical cancer incidence more than a standard three-dose program that vaccinates fewer women," said Aimée R. Kreimer, PhD, lead author and investigator in NCI’s Division of Cancer Epidemiology and Genetics. "The main question will be whether the duration of protection from fewer doses is adequate."
Kreimer emphasized that findings from this study of the Cervarix vaccine in women in Costa Rica may not be relevant for all populations, such as those in which HIV infection, malnutrition, or endemic diseases may influence the immune response. In addition, it is not known whether the same results would be obtained with the other FDA-approved HPV vaccine, Gardasil, because the vaccine formulations are different.

"Further studies are needed to confirm our findings in other populations as well as to quantify the duration of protection for fewer than three doses," said Kreimer. "If other studies confirm that fewer than three doses provide adequate protection against persistent cervical HPV 16 and 18 infection, we may be one step closer to prevention of cervical cancer, especially for women in resource-poor settings, where the need is greatest."

It is important to note that regulatory agencies have approved the HPV vaccine based on prevention of cervical precancers, not persistent infections. From studying the natural history of HPV and cervical cancer, experts know that persistent infections are first steps toward precancer. Furthermore, vaccine recommendations take into consideration many factors and studies. In the United States, the CDC's Advisory Committee on Immunization Practices determines federal recommendations regarding vaccination.

9/13/11

References

**Heavy Rains, Flooding Exacerbating Cholera Epidemic In West And Central African Countries**

A cholera epidemic in West and Central Africa, which is being worsened by heavy rains and flooding, has already caused nearly 40,000 cases this year in Cameroon, Chad, Niger and Nigeria, killing almost 1,200 people in the countries adjacent to the Lake Chad Basin, according to the U.N. Office for the Coordination of Humanitarian Affairs (OCHA), *VOA News* reports.

A lack of access to potable drinking water and proper sanitation facilities, combined with a transient population and heavy rains, are helping the disease spread among countries in the Lake Chad Basin region, the news service notes. "[T]he WHO says a death rate of higher than one percent indicates problems in the health system," VOA writes, adding, "Affected countries in the Lake Chad Basin, such as Cameroon and Chad, are reporting death rates of more than three percent" (Look, 9/12).

**U.S. Support To Haiti In Wake Of Ongoing Cholera Epidemic 'Remains Unfailing'**

A *VOA News editorial* says U.S. support to Haiti since the early days of an outbreak of cholera, which has affected more than 439,600 people since it was first detected almost a year ago, "remains unfailing." The editorial continues, "To date, the U.S. government has spent more than $75 million on improved water, sanitation and hygiene facilities, ... has established and operated treatment centers and trained Haitian health care workers in preventing, diagnosing and treating cholera," among other treatment, prevention and monitoring initiatives. "While some humanitarian groups are gradually reducing their operations in Haiti, the U.S. remains focused on giving the Haitian government the aid and tools needed to prevent and treat this potentially deadly disease," the editorial says, adding, "The medical and public health response has been effective in limiting deaths associated with the disease" (9/12).

**Kenyan Clash in Debate to Bring Sex Education Into Schools** *(long)*

Sex has long been a taboo subject in Kenya. As the government, school officials, religious authorities and parents debate whether there should be formal sex education in schools, teen pregnancy and HIV are on the rise.

by Joanne Wanjala Reporter, Thursday—September 15, 2011

NAIROBI, KENYA — Sofia Atieno is just 16, but she is already the mother of a 1-year-old son, Erastus Owino.

Atieno, an orphan, lives in Mathare, a sprawling slum of Nairobi, the capital, where she takes care of her son and her younger brother, Thomas Omondi, 13. She says her mother died when she was 7, and her father died in 2009, both after short illnesses.

She says she became sexually active after her father died. She was in seventh grade. Atieno says her father never talked openly about sex, a taboo subject in Kenya.
“How could he even start talking to me about sex?” she asks shyly.

But she says that his absence allowed her to become more promiscuous. The following year, 2010, she got pregnant and dropped out of school.

She says the father of her unborn child vanished, so she has had to take care of their son all by herself. She does casual labor in the slums to earn money, taking on odd jobs like doing laundry and cleaning.

She says the three of them survive on her earnings of about 200 shillings KES ($2.10 USD) per day. She pays 800 shillings KES ($8.40 USD) to rent a tiny room in the slum.

Atieno didn’t receive sex education in school. She says sex is not talked about openly here because it is considered an “immoral topic,” according to the religious teachings administered during Christian religious education, a subject taught within the school curriculum.

“I lost my virginity when I was 13, even though I knew nothing much about sex,” she says with her eyes fixed on the ground.

While sex remains a taboo topic in Kenyan and African society as a whole, the increasing rates of HIV, AIDS, sexually transmitted infections, STIs, and teenage pregnancies have prompted teachers to call for formal sex education in schools.

Last month, about 150 students from Fish High School in Kenya’s Coast province were forced to go home after contracting an STI that spread like bushfire within the school, according to a report aired on a local television channel.

In response, nongovernmental organizations, NGOs, have tried to introduce educational programs in schools. Religious authorities vary in their views of sex education, but they agree it should be approached with caution. As society slowly shifts its view, younger parents say they are more open to discussing sex with children than older parents are. The government has not announced any plans to include sex education in the formal school curriculum, and officials tend to shy away from the topic.

About 12 percent of female and 20 percent of male respondents ages 15 to 49 said they had had sexual intercourse by age 15, according to the most recent Kenya Demographic and Health Survey from 2008-2009. Nearly half of females and more than half of males had sex by age 18. Nearly all surveyed knew of at least one method of contraception. More than 13,000 girls drop out of school each year, accounting for 31 percent of all dropout rates among girls here, according to the Forum for African Women Educationalists, a Pan-African NGO.

In Kenya, about half of males and females ages 15 to 24 have comprehensive knowledge of HIV, according to UNICEF. Whereas nearly 65 percent of males in this age group used a condom last time they had sex with a partner they weren’t married to or living with, only 40 percent of females did.

Lillian Nyawira, a teacher and owner of Amazing KinderCare Academy in Nairobi, says that changes in societal norms and increased access to information through advanced technology demand that both parents and teachers take responsibility for talking to children about sexual matters from early stages of development to help them make informed choices.

“It is no longer a matter of silence because of moral degradation in the society and the fact that kids have access to information through different media and sometimes parents have no control over what they view,” she says.

She says kids in upper primary school have a right to know and learn about sex, especially with the blossoming rates of rape cases and HIV infections. She says that approaching the subject from a biblical standpoint could work for children younger than 10, who might not grasp all the concepts yet.

“This education should not only focus on abstinence, but also on the dangers of premarital sex,” she says.

Michael Gachuhu, the school director and a father of two, agrees with Nyawira that teachers should get involved. But he cautions against parents abandoning their responsibilities when it comes to educating their children about sex and leaving the task entirely to teachers.

“Teachers only complement what parents do, and there might be little that a school curriculum can do without the support of parents in modeling their children,” he says.

He says that religious and cultural authorities may not approve of openly discussing sex, but that it is high time to demystify the subject in school because of the way it has pervaded society. He says the approach will vary by age.

“Sex education should be introduced systematically at different levels in schools,” he says.

Religious authorities give mixed opinions when it comes to sex education, but most emphasize caution.
The Rev. Patrick Kanja, Catholic chaplain of the University of Nairobi, says that if sex must be taught in schools, then it should be done with the value, respect and the dignity that it deserves. He also says that the information must have a good Christian foundation.

“The issue of contraceptives, for instance, should be taught with the disclaimer that they are not good,” Kanja says.

On the other hand, the Rev. Henry Musuluma, pastor of the Assemblies for Christian Churches International, a local Protestant Church, says it is the right of the children to know and learn about sex and to understand that sex is God-given and should not be abused.

Rosemary Wangao, an accountant, says she never spoke with her son, Francis Otieno, 22, about sex when he was growing up.

“I have no control over what he does now because I never nurtured an open communications strategy ever since he was a child,” she says. “I even don’t trust what he does, especially when he is on Internet.”

She says this is because sex is taboo in Kenyan society.

“Sex has been and is still a taboo subject and talking about it openly may deem one immoral,” she says. “Perhaps if it is openly taught in schools in this era of so many sexually related problems, it will help our children know how to cope with such problems.”

But for many, perspectives seem to be changing.

Respah Kusienya, a Nairobi resident and mother of 7-year-old twins, Rozah and Zorah, says she has already started preparing her daughters about the topic. She says that if schools introduce sex education in the curriculum and parents also do their part, kids will be more open and will make informed choices.

“Yes, I think it is important for children so be educated on sex,” she says. “I feel it would be appropriate to talk to them about sex, STDs, HIV from age of 7 and above. As a parent, you can start off by educating what is relevant to their age and proceed on into more serious issues that can affect them before they start getting sexually active.”

In a recent study, 65 percent of youths sampled said they wanted sex education to be included in the formal school curriculum and parents to be involved in issues related to sexual health, according to the Center for the Study of Adolescents, CSA, a regional organization that promotes the health and development of young people through research, advocacy and capacity building.

Albert Obbuyi, CSA’s chief executive officer, calls sex education the vaccine for addressing all sexuality problems that children face from primary to high school because sexuality is a universal experience to all people. He says that the government isn’t doing enough.

“Although the government introduced the life skills curriculum in schools in 2008-09 as a measure towards sexuality education, advocacy initiatives to comprehensively address sexual and reproductive health in schools is still not sustainable,” he says.

Obbuyi says that CSA has tried to initiate programs in schools. In 2007, CSA launched a computer program called “The World Starts With Me” to promote sexual and reproductive health education in schools. It collaborated with the Ministry of Education and the Dutch World Population Foundation, an international nonprofit organization aimed at improving the quality of life in developing countries by ensuring sexual and reproductive health and rights for all.

“The program initially started with five schools in Nairobi but has so far reached out to 129 schools, covering Nairobi, Nyanza, Coast and Central regions,” he says. “We have been able to reach out to over 6,000 school-going youth both in primary and high school levels with the help of about 300 trained teachers.”

The game aims to improve and promote safer sexual behavior and delay the onset of sexual activity among young people, he says. Obbuyi says he is optimistic that if all Kenyan schools formalized a program like this, it could significantly contribute to addressing health and other social challenges that young people face as they grow up.

“Sexuality education may not solve all sexually related problems in the society but can help youths make informed decisions,” he says.

Obbuyi proposes using the UNESCO guidelines for sex education, which teaches children about the risks of sexual activities, contraceptives and the negative effects of abortion.

“It is about empowering them to make informed decisions,” he says.

Obbuyi says that CSA has showed no signs throughout the years of integrating sex education into the formal school curriculum.

For example, in 1997, then-President Daniel Arap Moi shelved a paper on sex education and family life that was to be presented in Parliament, saying it was not only immoral, but also bound to expose students to “tabia mbaya,” which means “bad manners” in Swahili.
Junior ministers in the Ministry of Education declined to comment on the current government’s position toward sex education. Curriculum developers from Kenya Institute of Education, a semiautonomous governmental organization, say they need permission to comment. The director hasn’t responded to permission requests.

**Bionor AIDS Injection Helps Patients Stay Off Pills in Study**

*By Simeon Bennett—Sep 14, 2011*

**Bionor Pharma ASA (BIONOR),** the Norwegian developer of an experimental AIDS treatment, said the injection lowered viral levels in patients’ blood and helped some of them stay off daily pills for more than a year.

As many as 30 percent of patients in a study of Bionor’s Vacc-4x were able to stay off antiretroviral therapy more than a year after they stopped, compared with 18 percent who got a placebo, the Oslo-based company said in a statement today. The results were presented at a conference in Bangkok.

The findings may help Bionor revive Vacc-4x after saying in October it would scrap the shot because six-month data showed it didn’t work, sending the stock down 81 percent. A month later the company reversed the decision after further analysis showed the treatment lowered viral levels. It now plans three more trials to see if it can improve on today’s results, including one combining Vacc-4x with Celgene Corp. (CELG)’s cancer drug Revlimid.

“We don’t see this as a standalone alternative to antiretroviral therapy,” Vidar Wendel-Hansen, Bionor’s chief medical officer, said in an interview. “What we do see is the long-term potential to train the immune system to take over the role of antiretroviral therapy. That’s the goal.”

Bionor was unchanged at 1.55 kroner at the close of trading in Oslo.

**‘Not as Compelling’**

Unlike the pills that are the mainstay of HIV treatment, Vacc-4x is a so-called therapeutic vaccine designed to fight the virus by marshaling the body’s immune system against it. While the shot hasn’t yet been shown to subdue the virus as well as antiretroviral therapy, regular injections that keep it at relatively low levels may save patients from the side effects and costs associated with pills.

The trial involved 135 patients who had been using anti-AIDS drugs to control HIV for at least six months. Two-thirds received six shots of Vacc-4x while taking their regular pills over 28 weeks, then stopped taking the drugs. The other third received an injection of water.

Six months later, those who got the shot had an average 70 percent reduction in the amount of virus in their blood compared with the level before they started pill therapy. More than a year after they went off treatment, 30 percent of them remained pill-free, compared with 18 percent of the placebo group.

“Several years ago I would have been tremendously excited” by the results, Michael Saag, director of the Center for AIDS Research at the University of Alabama at Birmingham, said in an e-mail.

“Now I find it interesting, but not as compelling,” Saag said. “The reason is that we have growing evidence that, even with no detectable virus among folks not on antiretroviral therapy, there is evidence of increased inflammation.” Even low levels of viral replication—which the pills control—could be harmful to patients in the long-term, according to Saag.

**Synthetic Drugs Now Second Most Popular Drugs: UN**

*Agence France Presse, (09.13.2011)*

Synthetic amphetamine-type stimulants (ATS) have surpassed heroin and cocaine to become the second most widely consumed drugs in the world, after marijuana, according to a study released Tuesday by the UN Office on Drugs and Crime (UNODC).

“ATS are attractive to millions of drug users in all regions of the world because they are affordable, convenient to the user, and often associated with a modern and dynamic lifestyle,” says the assessment. “Their risks are often underestimated in public perception.”

Increasingly, those risks include HIV/AIDS. “Injecting ATS use is also growing and increasing the risk of blood-borne diseases such as HIV/AIDS,” the report says. “In Thailand, injecting is the second-most common delivery system for ATS, while in New Zealand it is the most commonly injected drug. Injecting use is also now commonplace in some countries in Europe.”

Also troubling is the emergence of so-called analogue substances, which may be sold as “bath salts” or “plant food.” “Highly dangerous and as yet still deemed legal in many countries, these drugs remain widely available over the Internet,” UNODC warned.
“The ATS market has evolved from a cottage-type industry typified by small-scale manufacturing operations to more of a cocaine- or heroin-type market with a higher level of integration and organized crime groups involved throughout the production and supply chain,” UNODC chief Yury Fedotov said in a statement.

The volume of drugs seized is indicative of the growing problem. The number of methamphetamine pills confiscated by authorities in Southeast Asia grew from 32 million in 2008 to 133 million last year. To download the full report, visit http://www.unodc.org/documents/ATS/ATS_Global_Assessment_2011.pdf

**Bacterial STDs and Perceived Risk Among Sexual Minority Young Adults**

*Perspectives on Sexual & Reproductive Health Vol. 43; No. 3: doi:10.1363/4315811*, (09..2011) Christine E. Kaestle; Martha W. Waller

Because most sexual health interventions focus on the sexual risk behavior of heterosexuals, health practitioners lack information about the sexual health of sexual minority adults ages 18-26.

The authors of the current study assessed three indicators of sexual minority status—identity, behavior, and romantic attractions—in 10,986 young adults who took part in Wave 3 of the National Longitudinal Study of Adolescent Health (2001-02). Associations between these indicators and individuals’ perceived risk for STDs and actual STD infection were examined using logistic regression analyses. Data from the 1,154 respondents with current or recent bacterial STD infections were investigated to determine if they had underestimated their risk.

“Outcomes varied by sexual minority status indicator and by sex,” the authors found. For bisexual females, the odds of STDs were significantly higher than for heterosexual females (odds ratios=1.4), and females who reported being attracted to both sexes had significantly higher STD odds than those attracted to males only (1.8). None of the sexual minority status indicators predicted STDs for males. Among respondents with an STD, females who reported only same-sex relationships were more likely to think they were at very low risk for infection compared to females reporting only opposite-sex relationships (17.2). Homosexual females had a higher likelihood of this outcome than heterosexual females (19.7).

“Health practitioners need to assist sexual minority young adults, particularly females, in understanding their risk for STDs and in taking safer-sex precautions,” the authors concluded.

**Number Of Breast, Cervical Cancer Cases Rose Significantly Over Past 30 Years, Global Study Says**

"The number of cases and deaths from breast and cervical cancer is rising in most countries across the world, especially in poorer nations where more women are dying at younger ages, according to a global study of the diseases" by researchers from the Institute for Health Metrics and Evaluation (IHME) at the University of Washington, Reuters reports. Between 1980 and 2010, breast cancer cases more than doubled worldwide, rising from 641,000 cases in 1980 to 1.6 million cases in 2010, while deaths from breast cancer rose from 250,000 a year to 425,000 a year, according to the study, which was published in the Lancet on Thursday, Reuters notes. The "number of cervical cancer cases rose from 378,000 cases in 1980 to 454,000 in 2010, and deaths from cervical cancer rose at almost the same pace as cases," the news service writes (Kelland, 9/15). The majority of new cases occurred among women under age 50 in low-income nations, BBC News writes (Briggs, 9/14).

"Officials estimate that about 343,000 women every year die in childbirth, most in the developing world. In comparison, breast cancer kills 425,000 women a year while cervical cancer kills about 200,000," the Associated Press/CBS News notes (9/14). "Women in richer countries fared better due in part to screening, medicines, anti-smoking policies and vaccines," BBC reports (9/14). "The researchers said the findings added urgency to calls from public health experts to world leaders to make cancer screening, treatment and education a priority in poor nations," according to Reuters (9/15).

**Follow-Up Study Of HIV Vaccine Trial Provides Clues For Continued Research**

"After two years of analyzing the results of the largest AIDS vaccine clinical trial ever held—called RV144—researchers say they have found two ways the immune system can respond, which could predict whether those inoculated will be protected or are more likely to become infected with HIV," CNN’s health blog "The Chart" reports. The results were presented at the AIDS Vaccine 2011 conference being held this week in Bangkok, Thailand (Young, 9/13).

The large study, which concluded in 2009 in Thailand, showed that during the first year of vaccination, protection was as high as 60 percent but it quickly declined to 31 percent overall, BMJ notes (Roehr,
9/15). According to PlusNews, "Vaccine recipients with high levels of one type of antibody response had the lowest rate of HIV infection, and those with high levels of another type had the highest rate of infection." Barton Haynes of Duke University, who coordinated the follow-up study of the trial data, said the information is a "hypothesis generator" that would inform future research, PlusNews reports (9/14).

**Experimental Malaria Vaccine Shows Positive Results Among Children In Small Burkina Faso Study**

"An experimental malaria vaccine tested on children in Burkina Faso has shown 'a high level of efficacy' in protecting against the disease, a study published in" Thursday's New England Journal of Medicine said, according to Agence France-Presse. The research, which "was initially planned to study the safety and immune response of the vaccine, known by the name MSP3 ... was led by scientists from the National Center for Research and Training on Malaria in Burkina Faso, the London School of Tropical Medicine and Hygiene and the Paris-based Pasteur Institute," the news agency writes.

"In the study, 45 children aged 12-24 months were randomized into three groups receiving doses of either 15 or 30 micrograms of the experimental malaria vaccine, or the control vaccine against Hepatitis B," AFP reports. "It found children who received the new vaccine at either dose had incidence rates three to four times lower than children who did not, 'yielding efficacy rates of 64 and 77 percent protection against clinical malaria,' the journal article said," according to the news agency, which adds that larger trials are needed to verify the results (9/14).

**Avoiding fatal responses to flu infection**

Most of the time, being ill with the flu is little more than a nuisance. Other times, it can spark an exaggerated immune response and turn deadly. Researchers reporting in the September 16th issue of the journal Cell, a Cell Press publication, have now traced the origins of this severe immune response—called a cytokine storm—to its source.

Cytokines are the chemical signals that drive inflammation, and cytokine storms are thought to be the cause of many of the deaths attributed to the 1918 worldwide influenza pandemic and to the more recent outbreaks of swine and bird flu infection. The new study provides encouraging news by offering the foundations for a completely new kind of flu therapy.

"We are showing for the first time that you can actually separate the deleterious events from those needed to control the virus," said Hugh Rosen, senior author of this study, from The Scripps Research Institute.

"It had been thought for a long time that all injury from influenza was due to the virus itself, consequently, and rationally, the focus was on developing antiviral drugs," said study co-author Michael Oldstone, also of Scripps.

The new results suggest that drugs aimed at the dangerous immune response may offer a life-saving new line of defense, by protecting infected hosts from themselves. Another bonus is that such an approach doesn't put the same pressure on viruses to adapt and develop drug resistance.

The cytokines associated with flu infection were thought to come from virus-infected cells found primarily in the lungs and nasal passages. The authors find that the cytokines are instead released from the endothelial cells that line blood vessels. A protein found on the surface of endothelial cells, called Sphingosine-1-phosphate receptor (S1P1), is essential for flu-associated cytokine storms.

In mice treated with a molecule that targets S1P1, cytokine production and the early signs of inflammation are suppressed. As a result, the animals are much more likely to survive infection with H1N1 swine flu virus. Notably, several companies are already testing S1P1-targeted drugs in clinical trials, the researchers say.

"Now that we know where cytokines come from and have isolated the specific receptor-based mechanism, it is likely that a single oral dose of a compound can be developed that will provide protection from cytokine storm early in infection," Rosen says.

That's not to say that antiviral drugs will be a thing of the past. Rosen and Oldstone suggest that the most promising therapies of the future would include a combination of drugs designed to protect against cytokine storms and tackle viruses head-on.

Teijaro et al.: "Endothelial Cells Are Central Orchestrators of Cytokine Amplification during Influenza Virus Infection."
Breaching the Blood-Brain Barrier: Finding May Permit Drug Delivery to the Brain for Alzheimer’s, Multiple Sclerosis and Brain Cancers

ScienceDaily (Sep. 14, 2011) — Cornell University researchers may have solved a 100-year puzzle: How to safely open and close the blood-brain barrier so that therapies to treat Alzheimer’s disease, multiple sclerosis and cancers of the central nervous system might effectively be delivered.

The researchers found that adenosine, a molecule produced by the body, can modulate the entry of large molecules into the brain. For the first time, the researchers discovered that when adenosine receptors are activated on cells that comprise the blood-brain barrier, a gateway into the blood-brain barrier can be established.

Although the study was done on mice, the researchers have also found adenosine receptors on these same cells in humans. They also discovered that an existing FDA-approved drug called Lexiscan, an adenosine-based drug used in heart imaging in very ill patients, can also briefly open the gateway across the blood-brain barrier.

The blood-brain barrier is composed of the specialized cells that make up the brain’s blood vessels. It selectively prevents substances from entering the blood and brain, only allowing such essential molecules as amino acids, oxygen, glucose and water through. The barrier is so restrictive that researchers couldn’t find a way to deliver drugs to the brain—until now.

"The biggest hurdle for every neurological disease is that we are unable to treat these diseases because we cannot deliver drugs into the brain," said Margaret Bynoe, associate professor of immunology at Cornell’s College of Veterinary Medicine and senior author of a paper appearing Sept. 14 in the Journal of Neuroscience. Aaron Carman, a former postdoctoral associate in Bynoe’s lab, is the paper’s lead author. The study was funded by the National Institutes of Health.

"Big pharmaceutical companies have been trying for 100 years to find out how to traverse the blood-brain barrier and still keep patients alive," said Bynoe, who with colleagues have patented the findings and have started a company, Adenios Inc., which will be involved in drug testing and preclinical trials.

Researchers have tried to deliver drugs to the brain by modifying them so they would bind to receptors and "piggyback" onto other molecules to get across the barrier, but so far, this modification process leads to lost drug efficacy, Bynoe said.

"Utilizing adenosine receptors seems to be a more generalized gateway across the barrier," she added. "We are capitalizing on that mechanism to open and close the gateway when we want to."

In the paper, the researchers describe successfully transporting such macromolecules as large dextrans and antibodies into the brain. "We wanted to see the extent to which we could get large molecules in and whether there was a restriction on size," Bynoe said.

The researchers also successfully delivered an anti-beta amyloid antibody across the blood-brain barrier and observed it binding to beta-amyloid plaques that cause Alzheimer’s in a transgenic mouse model. Similar work has been initiated for treating multiple sclerosis, where researchers hope to tighten the barrier rather than open it, to prevent destructive immune cells from entering and causing disease.

Although there are many known antagonists (drugs or proteins that specifically block signaling) for adenosine receptors in mice, future work will try to identify such drugs for humans.

The researchers also plan to explore delivering brain cancer drugs and better understand the physiology behind how adenosine receptors modulate the blood-brain barrier.
**Key Signal That Prompts Production of Insulin-Producing Beta Cells Points Way Toward Diabetes Cure ***

ScienceDaily (Sep. 15, 2011) — Researchers at the Hebrew University of Jerusalem have identified the key signal that prompts production of insulin-producing beta cells in the pancreas—a breakthrough discovery that may ultimately help researchers find ways to restore or increase beta cell function in people with type 1 diabetes.

The work on the multi-year project was led by Prof. Yuval Dor of the Institute for Medical Research Israel-Canada of the Hebrew University, researchers from the Hadassah University Medical Center and researchers from the diabetes section of the Roche pharmaceuticals company. The study was published in a recent issue of the journal *Cell Metabolism*.

"Our work shows that as the glucose level is increased in the blood, it tells the beta cells to regenerate," says Dor. "It's not blood glucose per se that is the signal, but the glucose-sensing capacity of the beta cell that's the key for regeneration." This was the first time that this sensing of a high level of glucose has been shown to be the "trigger" that induces beta cells to regenerate.

In persons suffering from type 1 (juvenile) diabetes, the immune system launches a misguided attack on the insulin-producing beta cells, resulting in the cells’ decline of insulin production and eventual loss of function. Without insulin, the body’s cells cannot absorb glucose from the blood and use it for energy. As a result, glucose accumulates in the blood, leaving the body’s cells and tissues starved for energy. That’s why people with the disease must inject insulin and monitor their blood glucose levels diligently every day. To cure type 1 diabetes, it will be necessary to develop methods to increase beta cell replication and mass, hence the potential therapeutic importance of the current study.

In their work, Dor, along with co-lead author Prof. Benjamin Glaser of the Hadassah University Medical Center, used a genetic system to destroy 80 percent of the insulin-producing cells in the pancreases of adult mice, rendering the mice diabetic.

When the researchers compared these mice with control mice, they found that those mice with diabetes and elevated blood glucose levels had regenerated a greater number of new beta cells than mice without diabetes, suggesting that glucose may be a key player in beta cell regeneration. But the researchers further found that a glucose-sensing enzyme in the cells, glucokinase, is the key molecule that triggers the beta cell regeneration.

"This means that the more work that beta cells are required to do (that is, the more ‘stressed’ they are), the more of themselves they make," said graduate student Shay Porat, who, along with fellow graduate student Noa Weinberg, spearheaded the study, which was funded with the support of the Juvenile Diabetes Research Foundation (JDRF). .

Because this study showed that regeneration depends on glucokinase levels, the finding may pave the way for developing a new kind of drug to modulate glucokinase or other steps in the glucose-sensing pathway to direct beta cells down the path of regeneration and replication.

And, should a mechanism be discovered that prevents the immune system from attacking beta cells in the first place, as occurs among diabetics, the combined treatment could help pave the way towards a full cure for type 1 diabetes.

Further research in this area is proceeding, with the eventual goal of progressing towards human clinical trials.

**Journal Reference:**

**Copper Reduces Infection Risk by More Than 40 Per Cent, Experts Say**

ScienceDaily (July 1, 2011) — Professor Bill Keevil, Head of the Microbiology Group and Director of the Environmental Healthcare Unit at the University of Southampton, has presented research into the mechanism by which copper exerts its antimicrobial effect on antibiotic-resistant organisms at the World Health Organization’s first International Conference on Prevention and Infection Control (ICPIC).
'New Insights into the Antimicrobial Mechanisms of Copper Touch Surfaces' observes the survival of pathogens on conventional hospital touch surfaces contributes to increasing incidence and spread of antibiotic resistance and infections. Keevil proposes antimicrobial copper surfaces as one way to address this, since they achieve a rapid kill of significant bacterial, viral and fungal pathogens.

He reported studies on dry surfaces with a range of pathogens, concluding that: "Copper’s rapid destruction of pathogens could prevent mutational resistance developing and also help reduce the spread of antibiotic resistance genes to receptive and potentially more virulent organisms, as well as genes responsible for virulence. Additionally, copper touch surfaces could have a key role in preventing the transmission of healthcare-associated infections. Extensive laboratory tests have demonstrated copper’s antimicrobial efficacy against key organisms responsible for these infections, and clinical trials around the world are now reporting on its efficacy in busy, real-world environments."

The latest trial—conducted in intensive care units at three facilities in the United States—has shown that the use of antimicrobial copper surfaces in intensive care unit rooms resulted in a 40.4% reduction in the risk of acquiring a hospital infection.

The study, funded by the US Department of Defense, was designed to determine the efficacy of antimicrobial copper in reducing the level of pathogens in hospital rooms, and whether such a reduction would translate into a lower rate of infection.

Researchers at the three hospitals involved in the trial—Memorial Sloan Kettering Cancer Center in New York, the Medical University of South Carolina (MUSC) and the Ralph H. Johnson VA Medical Center, both in Charleston, South Carolina—replaced commonly-touched items such as bed rails, overbed tray tables, nurse call buttons and IV poles with antimicrobial copper versions.

Data presented today by trial leader Dr Michael Schmidt, Professor and Vice Chairman of Microbiology and Immunology at MUSC, at ICPIC, demonstrated a 97% reduction in surface pathogens in rooms with copper surfaces, the same level achieved by "terminal" cleaning: the regimen conducted after each patient vacates a room.

Dr Schmidt said of the results: "Bacteria present on ICU room surfaces are probably responsible for 35-80% of patient infections, demonstrating how critical it is to keep hospitals clean. The copper objects used in the clinical trial supplemented cleaning protocols, lowered microbial levels, and resulted in a statistically significant reduction in the number of infections contracted by patients treated in those rooms."

The spirit is willing, but... sex in the HIV-positive over-50s
Gus Cairns
Published: 16 September 2011
Although the average age of the HIV-positive population is increasing, in both richer and poorer countries, and though sex between older people has often been cited as a possible risk factor for HIV, there has been surprisingly little investigation into the sex lives of people with HIV who are over the age of 50.

A small qualitative study presented to the Tenth AIDS Impact conference of 38 people with HIV in Montreal, Canada, equally balanced between different affected groups, sought to establish patterns of sexual activity in this population and to ask people about the factors behind their behaviour.

Its primary finding was that HIV-positive people, at least in this group, were having relatively little sex – and not always by choice. It also found clear differences between men and women, gay and straight, and injecting drug user (IDU) and non-IDU respondents.

Presenter Isabelle Wallach of the Clinique l’Actuel in Montreal told the conference that in Canada, in 2008, 15.3% of new HIV diagnoses involved people aged 50 years and over, and one-quarter of the HIV-positive population is now over 50. Her team’s study aimed therefore to document the experiences of sex and relationships in a group of people with HIV who were over 50, with a view to shedding light on the intersection of HIV, sex and ageing.

The study consisted of individual semi-structured in-depth interviews, with an average duration of two and a half hours, in 38 people with HIV aged 50-74 years.

Twelve gay men, twelve heterosexual men, and 14 women took part in the study. Twelve participants were of non-white ethnicity and eight had acquired HIV through injecting drug use.

Out of the 38 interviewees, only 13 were currently in a relationship, and while nine said they were happy in it, four stated they were having difficulties in the relationship.
Of the 25 single people, eleven stated that it was their choice to be single, while the other 14 said they were unwillingly so and would like a relationship. There was a clear gender divide here: while seven of the women were single by choice, only one of the men was.

Only five out of the 38 interviewees defined themselves as ‘actively sexual’ and 17 stated they were not having sex at all. Again, there was a clear sexuality and gender divide here: ten of the 14 women and seven out of eight injecting drug users said they were having no sex, but none of the gay men.

This left 16 interviewees who were having some sex but described their sex lives as "slow or not very active".

The qualitative interviews shed a lot of light on participant’s views of sex.

Six stated that fear of transmitting HIV was important to them while four stated the death of a partner to AIDS had changed their attitude towards sex (none of the qualitative attitudes explored are exclusive: participants could hold a number of different attitudes).

Stigmatisation and disclosure was one of the most common reasons cited for problems with sex. One 65-year-old gay man said “Nowadays, sometimes, I meet someone, if I tell him ‘I am positive’, whoops, he is gone.”

Six stated that difficulties they or their partner had with condoms were a reason they had little sex. One woman (59 years old) said that her male partner had never used condoms, having come out of an 18-year relationship, and could not maintain an erection while using one. A 60-year-old heterosexual man said he had experienced resistance to condom use in female partners: “Some women take it as an insult [when I say] we must have safe sex. One said, ‘Who do you think I am?’”

Some people were reconciled to the fact that the need for sex diminishes with age, as does sexual performance. One 62-year-old women in a relationship said: “It’s been five years since we met and, you know, it’s more ‘tenderness love’ these days.”

Others were less happy about it. Some mourned the fact that age brings with it less power to seduce: “Once we get older we get less looked at,” said one gay man who had reached that age. Others saw it as outright discrimination: “I have already approached some people and...I get told ‘What is it that you want? You’re old’”, said one 56-year-old gay man.

Unhappiness about the lack of sex and relationships was, however, balanced in many cases by a positive attitude towards being single and a determination not to let it spoil life. “If you delude yourself about really wanting it, you’re more disappointed because you don’t have it. If it happens, it happens,” said one 65-year-old gay man. A 53-year-old woman said “You’ve lived such intense things that it can’t be an obsession. You can’t want it at all costs ... just being alive is already something.”

With qualitative studies like this, reaching hard conclusions about older positive people and sex is not the point, but Isabelle Wallach commented that the clear gender, sexuality and transmission group divides that came up even in this small study suggested further avenues of exploration. While many participants regarded their sex lives (or lack of them) with detachment, others were struggling with problems of both HIV status and ageing. More research into sexuality in the older person with HIV was warranted.

Reference

PEPFAR Announces Largest Study of Combination HIV Prevention
Office of the Spokesperson
Washington, DC
September 14, 2011
Today, the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR) announced awards for a new initiative totaling $45 million over four years to examine the effectiveness of combination approaches to HIV prevention. These evaluations of combination prevention will be the largest and most robust to date. Data gathered will help partner countries to strengthen their efforts to prevent new infections and save lives.

To quickly build an evidence base, PEPFAR will support three awards. With funding from the National Institutes of Health (NIH), the London School of Hygiene and Tropical Medicine will partner with the NIH-funded HIV Prevention Trials Network to examine a strategy linking household-based HIV testing to universal community-based HIV treatment in Zambia and South Africa. The Harvard School of Public Health will receive funding through the Centers for Disease Control and Prevention to evaluate the impact on HIV incidence of expanding population coverage of an integrated set of HIV prevention
interventions in Botswana. Through an existing USAID award, Johns Hopkins University will evaluate the impact of an integrated set of biomedical, behavioral and structural prevention interventions to reduce HIV incidence in the Iringa region of Tanzania.

Combination prevention uses a suite of mutually reinforcing interventions to address the risks of HIV transmission and acquisition as thoroughly and strategically as possible. Ambassador Eric Goosby, U.S. Global AIDS Coordinator, commented, “In light of recent research establishing the preventive effect of antiretroviral treatment, antiretroviral-based interventions will be a key component of the combination approaches studied.”

The evaluations will be critical to U.S. efforts to maximize the impact and efficiency of investments in order to save as many lives as possible. The studies will begin in 2011 and 2012, and implementation and evaluation will be coordinated by a linked to the PEPFAR Scientific Advisory Board. This coordinated approach will help address critical research questions in a timely fashion. For additional information, please visit the following links:

www.PEPFAR.gov/sab
www.usaid.gov/our_work/global_health/aids
www.cdc.gov/globalaids
www.niaid.nih.gov/topics/hivaids/Pages/Default.aspx

Crown applies to intervene in HIV criminalization case

HIV CRIMINALIZATION / A 'kick in the face' for those working on the issue, say activists

Danny Glenwright / Toronto / Thursday, September 15, 2011

Ontario’s attorney general has applied to intervene in a Supreme Court of Canada decision that activists say could make it easier for courts to convict HIV-positive Canadians who don’t disclose their status to sexual partners.

In a document submitted on Sept 9, the attorney general’s office noted there was “uncertainty and unfairness” in current laws.

It is calling for a consent-based framework rather than the current legal approach, which has been applied unevenly and has allowed judges to convict HIV-positive Canadians even when they haven’t passed on the virus.

“This is a kick in the face for people working on this issue,” says Tim McCaskell, a member of the AIDS Action Now steering committee. “This basically makes disclosure a requirement for any kind of interaction. As we know from Bill Clinton, it’s difficult to know what’s sex and what’s not. If we give someone a peck on the cheek, is it sex?”

McCaskell is frustrated with Ontario Attorney General Chris Bentley, who last year told Xtra he would consult members of the community about creating prosecutorial guidelines to ensure less confusion in the courts.

In several instances, people have been charged with assault or aggravated assault for spitting or scratching someone, while others have been charged with attempted murder because they did not disclose their HIV status before a sexual encounter, even when a condom was used.

“This goes in the completely opposite direction,” says McCaskell of the request to intervene in two cases from Courts of Appeal in Manitoba and Quebec, which will be appealed at the Supreme Court. “This would mean that if significant risk was no longer a criterion, then any HIV person who didn’t disclose in almost any circumstances could be prosecuted.”

Current Canadian law around HIV criminalization dates back to the 1998 Supreme Court Cuerrier decision, which ruled that knowingly exposing a sexual partner to HIV amounts to aggravated assault. This means people living with HIV have a legal duty to disclose if they could expose a partner to a significant risk of transmission.

However, prosecutorial guidelines to define what constitutes a significant risk have never been formalized, which has led to unfairness, something Bentley’s office recognized in the application.

A 2010 decision in the Manitoba Court of Appeal acquitted an HIV-positive man for sexual encounters in which a condom was used, or when a condom was not used but he had an undetectable viral load. The Court found neither was a “significant risk.”

Similarly, a Quebec Court of Appeal acquitted an HIV-positive woman who had sexual intercourse on one occasion without disclosing her status. Neither decision is binding in the rest of Canada and prosecutors in both cases applied for an appeal to the Supreme Court.
Bentley's office has applied to intervene in these cases, asking to remove the criterion of “significant risk.”

It stated in its application “the issues at the heart of these appeals are very important to the administration of justice.

“The task for the Court in these cases will be to devise a workable test that provides clarity, protects the public as best as possible and promotes certainty about the meaning of consent to sexual activity.”

The application notes that Ontario has a large number of criminal prosecutions and the highest number of HIV-positive people in Canada.

Cecile Kazatchkine, a policy analyst with the Canadian HIV/AIDS Legal Network, calls the decision to intervene in these cases a “radical move” that would lead to more HIV-positive people behind bars and have no impact on HIV prevalence rates.

Canadian HIV/AIDS Legal Network policy analyst Cecile Kazatchkine calls the Crown's decision a radical move.

“It would provide more clarity, but it would provide even more unfairness as well,” she says. “It could possibly amount to discrimination against people living with HIV. It means everyone living with HIV in Canada who cannot prove they disclosed their status may be at risk of going to jail, even in cases where they used reasonable precautions to protect their partner.”

She says Bentley has disregarded scientific advancements since the original 1998 Supreme Court decision.

“It is quite contradictory and doesn’t make sense,” she says.

Not true, says Glen Murray, Liberal MPP for Toronto Centre and a founding member of the Canadian AIDS Society.

“I’m very sensitive to this,” says Murray, who asked activists to have patience with the attorney general. “It’s a very complex set of decisions, a complex science, because you’re talking about levels of risk that are interpreted differently.”

Murray says Bentley has assured him that his office will listen to the concerns of McCaskell’s steering committee and pursue evidence-based guidelines.

Bentley’s office refused to comment until after the application has been reviewed.

“We are in a difficult situation because we are in a writ period,” says Murray. “I can’t act directly in my elected post because we’re in an election right now.”

But McCaskell thinks Ontario should immediately withdraw its request for intervention at the Supreme Court or intervene for a scientifically accurate assessment of significant risk.

Anything else, he says, is unacceptable.

“If you give somebody a blowjob in the park and then you get charged with sexual assault because you didn’t give the guy your medical resumé? This is bizarre, but that’s exactly what this is opening up.”

D.C. Students to Be Tested on Sex Education

Washington Post, (09.15.2011) Bill Turque

Students in D.C. public schools soon will undergo health education assessments as a way to guide instruction on topics such as HIV, STDs, contraception, and drug use. The 50-question exam, to be introduced next spring, will be the nation’s first statewide standardized test on health and sex education, according to the Office of the State Superintendent of Education, which developed the assessment for grades five, eight and 10.

The District has some of the country’s highest rates of STDs, teen pregnancy, and childhood obesity. While periodic surveys have measured student attitudes toward risky behavior, the new test will help inform educators’ understanding of what the system’s 75,000 students know and why they behave as they do.

“We don’t know as a system or as a city what knowledge kids have about these topics,” said Brian Pick, deputy chief of curriculum and instruction for D.C. Public Schools.

The assessment is based on a provision of the Healthy Schools Act of 2010, passed by the D.C. Council to address health concerns. Questions for the District exam have been adapted locally from a sample devised by the Council of Chief State School Officers to improve health education. The test also has been aligned with standards approved by the D.C. State Board of Education in 2008.

Adam Tenner, executive director of MetroTeenAIDS, welcomed the new assessment, citing the adage “what gets measured gets done.” At present, he said, “We are not preparing teachers or students to get good, high-quality sex and reproductive education.”
Cases of Breast and Cervical Cancer on Rise in Poor Nations

_The Guardian (London)_ (09.15.2011) Sarah Boseley

The number of cases and deaths from breast and cervical cancer is rising in most countries—particularly in the developing world, where more women are dying at younger ages, according to a new study.

“As high-income countries enjoy the benefit of early cancer screenings, drug therapies, and vaccines, the burden of breast and cervical cancer is shifting to low-income countries in Africa and Asia,” noted the first review of cancer data from 187 countries, which was conducted by Seattle-based Institute of Health Metrics and Evaluation. “Within those countries, more women are developing breast and cervical cancer during their reproductive years, adding more pressure on societies already suffering from high rates of infectious diseases and child mortality.”

“Global cervical cancer incidence increased from 378,000 (256,000-489,000) cases per year in 1980 to 454,000 (318,000-620,000) cases per year in 2010, a 0.6 percent annual rate of increase,” says the study. “Cervical cancer death rates have been decreasing but the disease still killed 200,000 (139,000-276,000) women in 2010, of whom 46,000 (33,000-64,000) were aged 15-49 years in developing countries.”

Of cervical cancer cases last year, 76 percent (344,535) were in developing nations. Over the 30-year period, the number of cases increased in all regions—except in high-income countries, and in east and south Asia, Eastern Europe, and southern Latin America, where they remained constant.

The number of women diagnosed with breast cancer increased by more than 2.5 times, from 641,000 to 1.6 million annually, from 1980 to 2010. The increase was seen in every country, with the highest growth rates in North Africa, the Middle East, Oceania, Southeast Asia, western sub-Saharan Africa, and central Latin America. The slowest rise was seen in developed nations.

As global efforts to combat maternal deaths continue to achieve success, “during the next 15 years, the ratio of maternal deaths to breast and cervical cancer deaths in developing countries in the reproductive age group will decrease from 2.3 to 1.3,” the study authors predicted.


Human Papillomavirus Vaccine and Behavioral Disinhibition

_Sexually Transmitted Infections Vol. 87: P. 349-353_, (06..2011) Christine L. Schuler; Paul L. Reiter; Jennifer S. Smith; Noel T. Brewer

The current study sheds light on the characteristics of parents who believe that vaccination against the STD human papillomavirus leads to sexual disinhibition and who think that females can safely stop undergoing Pap testing after HPV vaccination.

The data reported are chiefly from a survey conducted in October and November 2008. The subjects were parents of adolescent females living in areas of North Carolina with elevated rates of cervical cancer.

Of the 647 parents, only 101 (16 percent) endorsed the belief that teenage girls vaccinated against HPV are more likely to have sex. Parents holding such views were more likely to be older (odds ratio=1.89; 95 percent confidence interval 1.09 to 3.26), or to report conservative political views (OR=2.26; 95 percent CI 1.37 to 3.73).

Parents were less likely to believe vaccination would lead to sexual disinhibition if they had greater knowledge about the vaccine (OR=0.52; 95 percent CI 0.32 to 0.85), or if their daughters had received HPV vaccine (OR=0.31; 95 percent CI 0.17 to 0.57).

Only 30 parents (5 percent) mistakenly believed women could safely stop having regular Pap tests after receiving HPV vaccine. However, this belief was somewhat more prevalent among racial and ethnic minority parents (16 percent) and among fathers (13 percent).

“Few parents believed that HPV vaccine is likely to lead to increased sexual activity among females or reduce the need for vaccinated women to have regular Pap smears in the future,” the authors concluded. “Characterizing parents who hold beliefs in behavioral disinhibition is important, as clinicians encountering parents in practice may desire information about this population.”
UK Safety Review Leads to Lifting Ban on Gay Blood Donors
Published on Thursday, 15 September 2011 00:00
Written by Press Release
© Russell Kightley

A review by a UK safety advisory committee found that the type and timing of sexual activity—not sexual orientation—is the relevant risk factor for HIV transmission via donated blood, prompting health ministers in England, Scotland, and Wales to rescind the lifetime blanket ban on donation by men who have had sex with another man.

Henceforth, only men who have had anal or oral sex with another man in the previous 12 months (protected or unprotected) will be asked to refrain from donating blood. The US has a similar ban, in place since 1983. Australia, Japan, and Sweden, among others, have previously lifted their gay blood donation bans.

The UK committee also looked at blood donor selection criteria for sex workers—another group currently banned from giving blood—but is seeking further evidence before deciding whether to recommend a change.

Below is an edited excerpt from a press release issued by the UK Department of Health summarizing the review and the ensuing policy change. The full evidence report is available online at http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_129909.pdf.

Lifetime Blood Donation Ban Lifted for Men Who Have Had Sex with Men
September 8, 2011—The lifetime ban on blood donation by men who have had sex with men is to be lifted following an evidence-based review by the Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO).

The recommendation, which has been accepted by the health ministers in England, Scotland and Wales, means men whose last sexual contact with another man was more than 12 months ago will be able to donate, if they meet the other donor selection criteria. Men who have had anal or oral sex with another man in the past 12 months, with or without a condom, will still not be eligible to donate blood.

The change will be implemented by NHS Blood and Transplant (NHSBT) in England and North Wales on Monday 7 November and by the Blood Services of Scotland and Wales on the same date.

The Advisory Committee, comprised of leading experts in the field, joined by patient groups and key stakeholders, carried out a rigorous review of the latest available evidence including:
• the risk of infection being transmitted in blood;
• attitudes to compliance with the donor selection criteria; and
• improvements in testing of donated blood.

The Committee found the evidence no longer supported the permanent exclusion of men who have had sex with men.

The change means the criteria for men who have had sex with men will be in line with other groups who are deferred from giving blood for 12 months due to infection risks associated with sexual behaviours.

Public Health Minister Anne Milton said:
“Blood donations are a lifeline, and many of us would not have loved ones with us today if it was not for the selfless act of others.
“Our blood service is carefully managed to maintain a safe and sufficient supply of blood for transfusions. Appropriate checks based on robust science must be in place to maintain this safety record and the Committee’s recommendation reflects this. It is important that people comply with all donor selection criteria, which are in place to protect the health of both donors and transfusion recipients.”

Professor Deirdre Kelly from the Advisory Committee on the Safety of Blood, Tissues and Organs said:
“Around two million individuals generously donate blood every year in the UK to save patients’ lives. The SaBTO review examined the best available scientific evidence for UK blood donor selection in relation to sexual behaviours. Our recommendation takes account of new data that have become available since the last review in 2006, as well as scientific and technological advances in the testing of blood.

“Adherence to the donor selection criteria is vital to maintain the safety of the blood supply, and donors need to be assured that the criteria are evidence-based. We are confident that this change maintains the safety of the blood supply.”

Dr Lorna Williamson, NHS Blood and Transplant’s Medical and Research Director said:
“NHS Blood and Transplant’s priority as a blood service is to provide a safe and sufficient supply of blood for patients. We welcome this review and its conclusions. It gives us an opportunity to broaden our donor acceptance on the basis of the latest scientific evidence.

“It is essential that our donor selection rules are based on good evidence to maintain their credibility with donors, and this change gives us an updated policy that is proportionate to the current risk.

“The SaBTO review concluded that the safety of the blood supply would not be affected by the change and we would like to reassure patients receiving transfusions that the blood supply is as safe as it reasonably can be and amongst the safest in the world. There has been no documented transmission of a blood-borne virus in the UK since 2005, with no HIV transmission since 2002.”

Sir Nick Partridge, Chief Executive of Terrence Higgins Trust (THT), said:
“We welcome this decision, which is based on strong new evidence that all the experts are agreed on. These regulations will ensure the safety of the blood supply for all of us while also being fair and equal in their application. We can now detect blood-borne viruses earlier and have more understanding of them, and the change reflects that.

“The remaining deferral regulation for sexually active gay men is based on their heightened risk, as a group, of sexually acquired blood-borne viruses. Changing that depends on reducing gay men’s risk of HIV and other STIs to the same level as the rest of the population, and re-emphasising the vital importance of safer sex as far too many gay men still become infected with HIV each year. We will continue to campaign to improve gay men’s sexual health to a level where the regulations can be the same for all, regardless of sexuality.”

Coordinator of the UK Thalassaemia Society Elaine Miller said:
“Together with my colleague Dr Asa’ah Nkohkwo of the Sickle Cell Society, we have been members of the Blood Donor Selection Steering Group throughout the review of blood donor selection criteria related to sexual behaviour. We are completely satisfied that patient safety has been regarded as paramount throughout the review process. Patients should therefore be reassured that their safety will not be compromised by this change.

“We are fortunate enough to have an excellent system of blood donation in the UK which depends on the generosity and good faith of individual donors. Our members lives depend on this generosity and good faith and we are thankful to all those who come forward to donate blood.”

SaBTO considered the evidence for the current deferral of commercial sex workers (other than those with a history of intravenous drug use) at the same time, but concluded that additional data were needed before it could consider recommending a change.

Reference

T cells making brain chemicals may lead to better treatments for inflammation, autoimmune diseases
MANHASSET, NY—Scientists have identified a surprising new role for a new type of T cell in the immune system: some of them can be activated by nerves to make a neurotransmitter (acetylcholine) that blocks inflammation. The discovery of these T cells is novel and suggests that it may be possible to treat inflammation and autoimmune diseases by targeting the nerves and the T cells. The study was published this week in Science.

"The discovery that 2 percent of T cells can make acetylcholine under the control of nerves gives a new insight into how the nervous system regulates immunity," said Kevin J. Tracey, MD, president and chief executive officer of The Feinstein Institute for Medical Research, and principal investigator of the study. "The arrival of electrical signals from nerves activates these specialized T cells to produce the acetylcholine necessary to block inflammation, and protect against damage. It is possible to transfer these cells to cross-protect mice from inflammation, and to control these T cells by electrically stimulating the nerves directly."

The present study followed years of work from Dr. Tracey's lab that identified the role of the vagus nerve, named for its wandering course from the base of the brain to the liver, spleen and other organs, in blocking inflammation. Applying electrodes to stimulate the vagus nerve blocked the release of tumor necrosis factor (TNF) and other cytokines that underlie the tissue damage in arthritis, inflammatory bowel disease and other syndromes. Stimulating this nerve pathway led to increased production of acetylcholine, a neurotransmitter that binds to the alpha 7 nicotinic acetylcholine receptor. Activating this receptor on macrophages blocked the release of
immune molecules (the cytokines,) suggesting a novel strategy for developing anti-inflammatory agents.

But these results raised an important question because the nerve fibers in spleen release norepinephrine, another neurotransmitter, but not acetylcholine. The search for the cells that produce acetylcholine led these investigators to use "nude" mice, devoid of T cells. Then they examined the spleen cells that make acetylcholine and that led them to a subset of T cells. Transferring these acetylcholine producing T-cells into nude mice restored the vagus nerve circuit that blocked inflammation.

"Our results point to a population of acetylcholine-synthesizing memory T cells in spleen that is integral to the function of the inflammatory reflex, the nerve circuit that regulates inflammation and immunity," said Dr. Tracey. "It is as if these T cells occupy a nerve-like function in this important circuit."

It should be possible to target these T cells and to modulate this neural circuitry to develop therapeutic modalities for inflammatory and autoimmune diseases. In the future, it may be possible to isolate these T cells and exploit their anti-inflammatory activity. In the meantime, there is a more direct route to use this discovery for therapy. Rheumatoid arthritis patients in Europe are being studied in clinical trials where vagus nerve stimulators are implanted and turned on to stimulate this circuit and suppress inflammation.

Study Suggests HIV-1 Adapts in Response to Natural Killer-Cell-Mediated Immune Pressure

"Natural killer (NK) cells have an important role in the control of viral infections, recognizing virally infected cells through a variety of activating and inhibitory receptors. Epidemiological and functional studies have recently suggested that NK cells can also contribute to the control of HIV-1 infection through recognition of virally infected cells by both activating and inhibitory killer immunoglobulin-like receptors (KIRs). However, it remains unknown whether NK cells can directly mediate antiviral immune pressure in vivo in humans. ... [We] describe KIR-associated amino-acid polymorphisms in the HIV-1 sequence of chronically infected individuals, on a population level. We show that these KIR-associated HIV-1 sequence polymorphisms can enhance the binding of inhibitory KIRs to HIV-1-infected CD4(+) T cells, and reduce the antiviral activity of KIR-positive NK cells. These data demonstrate that KIR-positive NK cells can place immunological pressure on HIV-1, and that the virus can evade such NK-cell-mediated immune pressure by selecting for sequence polymorphisms, as was previously described for virus-specific T cells and neutralizing antibodies. NK cells might therefore have a previously underappreciated role in contributing to viral evolution."

Biochemical Cell Signals Quantified: Data Capacity Much Lower Than Expected, Scientists Find

ScienceDaily (Sep. 16, 2011) — Just as cell phones and computers transmit data through electronic networks, the cells of your body send and receive chemical messages through molecular pathways. The term "cell signaling" was coined more than 30 years ago to describe this process.

Now, for the first time, scientists have quantified the data capacity of a biochemical signaling pathway and found a surprise—it's way lower than even an old-fashioned, dial-up modem.

"This key biochemical pathway is involved in complex functions but can transmit less than one bit—the smallest unit of information in computing," says Ilya Nemenman, an associate professor of physics and biology at Emory University. "It's a simple result, but it changes our view of how cells access chemical data."

The journal Science is publishing the discovery by Nemenman and colleagues from Johns Hopkins University, including Andre Levchenko, Raymond Cheong, Alex Rhee and Chiaochun Joanne Wang.

During the 1980s, cell biologists began identifying key signaling pathways such as nuclear factor kappa B (NF-kB), known to control the expression of genes in response to everything from invading pathogens to cancer. But the amount of information carried by chemical messengers along these pathways has remained a mystery.

"Without quantifying the signal, using math and computer analysis to attach a number to how much information is getting transmitted, you have a drastically incomplete picture of what's going on," says Nemenman, a theoretical biophysicist.

He and Levchenko, a biomedical engineer, began discussing the problem back in 2007 after they met at a conference.
Levchenko developed microfluidic and measurement techniques to conduct experiments on biochemical signaling of the NF-kB pathway, and measure the transmissions occurring on the pathway in many thousands of cells at one time. Nemenman formulated the theoretical framework to analyze and quantify the results of the experiments.

"It was a shock to learn that the amount of information getting sent through this pathway is less than one bit, or binary digit," Nemenman says. "That's only enough information to make one binary decision, a simple yes or no."

And yet NF-kB is regulating all kinds of complex decisions made by cells, in response to stimuli ranging from stress, free radicals, bacterial and viral pathogens and more. "Our result showed that it would be impossible for cells to make these decisions based just on that pathway because they are not getting enough information," Nemenman says. "It would be like trying to send a movie that requires one megabit per second through an old-style modem that only transmits 28 kilobits per second."

They analyzed the signals of several other biochemical pathways besides NF-kB and got a similar result, suggesting that a data capacity of less than one bit could be common. So if cells are not getting all the information through signaling pathways, where is it coming from?

"We're proposing that cells somehow talk with each other outside of these known pathways," Nemenman says. "A single cell doesn't have enough information to consider all the variables and decide whether to repair some tissue. But when groups of cells talk to each other, and each one adds just a bit of knowledge, they can make a collective decision about what actions to take."

He compares it to a bunch of people at a cocktail party, with cell phones that have weak signals pressed to their ears. Each person is receiving simple messages via their phones that provide a tiny piece to a puzzle that needs to be solved. When the people chatter together and share their individual messages, they are able to collectively arrive at a reliable solution to the puzzle.

A similar phenomenon, called population coding, had been identified for the electrical activity of neural networks, but Nemenman and his colleagues are now applying the idea to bio-chemical pathways.

They hope to build on this research by zeroing in on the role of cell signaling in specific diseases.

In particular, Nemenman wants to analyze and compare the signaling capacities of a cancerous cell versus a normal cell.

"Cancerous cells divide when they shouldn't, which means they are making bad decisions," he says. "I would like to quantify that decision-making process and determine if cancer cells have reduced information transduction capacities, or if they have the same capacities as healthy cells and are simply making wrong decisions."

Nemenman uses a malfunctioning computer as an example. "If you push the 'a' key on your computer and a 'd' always shows up, that means the computer is misprogrammed but the information from your keystroke gets through just fine," he says. "But if you keep pressing the letter 'a' and different, random letters show up, that indicates a problem with the way the information is being transmitted."

Journal Reference:

A fifth of patients discontinue Atripla within a year, CNS side-effects the main reason
Michael Carter
Published: 19 September 2011
A fifth of patients who start antiretroviral therapy with Atripla switch to an alternative regimen within a year, according to UK data presented to the 51st ICAAC in Chicago. The main reason for changing therapy was central nervous system side-effects.

Antiretroviral treatment guidelines in the UK recommend a combination of efavirenz (Sustiva) and FTC/tenofovir (Truvada) for patients starting HIV treatment. These drugs are available in a combined pill, Atripla, which is taken once daily.

Therapy with Atripla usually achieves durable HIV suppression. However, like all anti-HIV drugs it can cause side-effects. Most notably, efavirenz has been associated with mood and sleep disturbances such as depression, vivid dreams and nightmares. Often these are mild and transient and lessen or disappear after the first few weeks of therapy. However, for a minority of patients, these side-effects are so severe that a change in treatment is necessary.

With well over 20 licensed antiretroviral drugs, most of which are taken once daily and have a mild side-effect profile, there are several effective alternatives to Atripla.
Therefore, investigators from the Chelsea and Westminster Hospital in London wanted to establish the proportion of patients who stopped taking Atripla in the first twelve months of therapy.

They undertook a retrospective study, reviewing the notes of 472 individuals who initiated first-line Atripla therapy. Most of the patients were men (94%), their median age was 37 years, three-quarters were white and 52% were gay.

Baseline viral load and CD4 cell count were 16,000 copies and 285 cells/mm$^3$ respectively. The study confirmed the effectiveness of Atripla. After six months of treatment, 92% of patients had an undetectable viral load, and this had increased to 98% at month twelve. These high rates of virological suppression were accompanied by a strengthening of immune function, with median CD4 cell count increasing to 387 cells/mm$^3$ after six months of therapy and 449 cells/mm$^3$ after a year of treatment.

Modest increases in total cholesterol were observed (4.3 mmol/l at baseline, to 4.7 mmol/l at month six and 4.8 mmol/l at month twelve), but triglycerides remained largely unchanged at approximately 1.5 mmol/l.

However, despite these impressive outcomes, a total of 89 patients (19%) discontinued Atripla within a year of starting therapy.

The median duration of treatment before discontinuation was approximately ten months (294 days). Almost half (48%) of patients who stopped taking Atripla did so three to twelve months after starting therapy with the drug. However, 36% of patients of the patients who discontinued therapy did so after more than one year after commencing Atripla treatment.

Central nervous system toxicities were the most common reason for stopping treatment with the drug (71%). The most common mood and sleep disorders were depression, dizziness, insomnia and nightmares.

Other causes of treatment discontinuation included liver toxicity (7%), rash (7%), and virological failure or resistance (7%).

“Individuals on Atripla are often required to switch antiretroviral therapy,” conclude the researchers, “the commonest reason in our cohort was for CNS [central nervous system] toxicity with the majority of cases occurring after more than 3 months.”

Reference
Zheng J et al. Discontinuation of tenofovir, emtricitabine and efavirenz as a single tablet regimen in HIV-1 infected individuals naïve to antiretroviral therapy. 51st Interscience Conference on Antimicrobial Agents and Chemotherapy, abstract H2-783, Chicago, 2011 (click here for the free abstract)

**Big falls in prevalence of protease inhibitor and triple-class resistance**

Michael Carter

Published: 19 September 2011

The prevalence of HIV resistance to protease inhibitors fell sharply between 2003 and 2010, according to a study presented to the 51st ICAAC meeting in Chicago.

Investigators from Monogram Biosciences analysed the profile of almost 70,000 stored blood samples with resistance to at least one antiretroviral drug. Over the seven years of the study, the percentage of samples with resistance to a protease inhibitor fell by half.

A marked fall was also observed in the proportion of samples with resistance to drugs in the three main antiretroviral classes.

HIV can develop resistance to the drugs used in antiretroviral therapy.

Early generations of anti-HIV drugs had a low genetic barrier to resistance, and demanded extremely high levels of patient adherence. This was especially the case with unboosted protease inhibitors, some of which needed to be taken two or three times daily and also had complicated food and drink restrictions.

However, since 2000 there have been significant improvements in HIV care, including the almost universal adoption of ritonavir-boosting of protease inhibitors. These drugs have a powerful anti-HIV effect. Even if they fail to suppress viral load, this rarely involves the emergence of drug-resistant virus.

Improved drugs in the nucleoside reverse transcriptase inhibitor (NRTI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) classes have been introduced, and completely new classes of antiretrovirals such as entry and integrase inhibitors have been developed. This means that an undetectable viral load is now the aim of HIV therapy, regardless of a patient’s treatment history or resistance profile.

Resistance tests are an integral component of HIV care and are used to guide the choice of suitable antiretroviral agents. Investigators from Monogram Biosciences wished to see if the prevalence of virus
resistant to any protease inhibitor, NRTI, or NNRTI had changed in recent years. They also wished to establish trends in the prevalence of single, dual and triple class resistance.

A total of 68,587 samples submitted to their laboratories between 2003 and 2010 for resistance testing were analysed.

In 2003, a total of 52% of samples had detectable resistance to a protease inhibitor. However, this had fallen to 26% by 2010 (p < 0.05).

“A strong trend of decreasing prevalence of protease inhibitor resistance was observed in the...database between 2003 and 2010,” comment the investigators.

Prevalence of NRTI resistance also fell from 77% to 70% (p < 0.05), and there was also a fall in the proportion of samples with evidence of resistance to NNRTIs (70% to 61%; p < 0.05).

Moreover, there was also a significant decline in the proportion of blood samples with triple-class resistance. Prevalence fell from 29% in 2003 to 11% in 2010 (p < 0.05). The prevalence of dual-class resistance also fell, from 40% to 35%. These falls were accompanied by an increase in the proportion of samples with resistance to one class of drug (31% to 54%; p < 0.05).

The resistance profile of samples with dual-class resistance was examined in more detail.

In 2003, resistance to NRTIs and NNRTIs was detected in 54% of samples; 37% exhibited resistance to protease inhibitors and NRTIs; and 9% showed evidence of resistance to protease inhibitors and NNRTIs.

By 2010, however, dual-class resistance profiles had changed significantly. Resistance to NRTIs and NNRTIs was evident in 70% of samples; protease inhibitor and NRTI resistance in 24%; and protease inhibitor and NNRTI resistance in 7%.

The investigators believe their results “may have important implications for ARV [antiretroviral] selection, clinical trial design and drug development.”

Reference
Paquet AC et al. Significant reductions in the prevalence of protease inhibitor and 3-class resistance: recent trends in a large HIV-1 protease/reverse transcriptase database. 51st Interscience Conference on Antimicrobial Agents and Chemotherapy, abstract H2-800, Chicago, 2011. (Click here for the abstract.)

Sangamo’s Blood-Cell Gene Therapy Fights HIV Without Drugs
September 18, 2011, 12:37 PM EDT
By Elizabeth Lopatto
Sept. 18 (Bloomberg)—Gene therapy developed by Sangamo Bioscience Inc. to mimic the blocking effect of white blood cells in people naturally immune to HIV helped six patients fight off the disease without drugs, a study showed.

In most people, the CCR5 gene acts as a receptor that shepherds HIV into the body’s cells. About 5 to 15 percent of the population, though, have one or two mutant copies of the gene that disrupts entry. The therapy by Richmond, California-based Sangamo used genetically modified white blood cells to imitate the effects of the mutant DNA, the study said.

The research, reported today at the Interscience Conference on Antimicrobial Agents and Chemotherapy in Chicago, may help patients who have HIV that’s resistant to current drugs, said Pablo Tebas, a researcher at the University of Pennsylvania in Philadelphia and a study investigator. It’s exciting because no serious adverse events were seen, he said.

The study found “these cells are going where they’re supposed to go,” Tebas said in an interview at the Chicago meeting. “At this stage it’s not a cure, and it’s a complicated treatment to expand to large segments of the population.”

Sangamo rose 1.2 percent, or 7 cents, to $6 in Nasdaq Stock Market composite trading on Sept. 16, after dropping 9.6 percent since the beginning of the year.

The most common side effect cited in the gene therapy study was a persistent smell of garlic, the researchers said. After the therapy, one patient who naturally had one copy of the mutant DNA maintained undetectable levels of HIV without drug use, the study found.

Mutant Percentages
About 10 percent of people have one normal and one mutant gene, and less than 5 percent have only mutant genes, Tebas said. The company has two trials ongoing using the modification method.

In the other five patients, the amount of HIV in their bodies first increased during a 12-week period in which they weren’t taking anti-viral drugs, and then the level dropped, according to the study. The patients were male, and ranged in age from 31 to 56. Three had been infected for about 20 years.
“We see a significant anti-viral effect,” said Samgamo Chief Executive Officer Edward Lanphier in a telephone interview. “That’s the big punchline here.”

In Sangamo’s process, doctors draw patients’ blood and remove white blood cells, also called T cells. They are sent to Sangamo and modified using naturally occurring proteins called zinc fingers that cut into patients’ DNA in the middle of the CCR5 gene. The modified cells are then returned to the patient through an infusion.

**Base of Immunity**
The therapy doesn’t remove the CCR5 protein from all of the patients’ cells, Tebas said. Instead, it provides a base of immunity that helps patients suppress the virus, he said.

The next step is to increase the number of modified cells in patients, he said.

Antiviral drugs, led by Atripla and Truvada, made by Gilead Sciences Inc., of Foster City, California, and Reyataz, sold by New York-based Bristol-Myers Squibb Co., generated $15.1 billion in worldwide sales last year, according to IMS Health Inc., a Norwalk, Connecticut-based industry research company.

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**Zimbabwe: 60 Percent of Local Cancer Cases HIV Related**
Tsungirirai Dhambuza
19 September 2011

ZIMBABWE records 7,000 new cancer cases annually and 60 percent of these are HIV related, the Health and Child Welfare Ministry has said.

Speaking at the National conference on cancer prevention and control Health and Child Welfare Deputy Minister Dr Douglas Mombeshora said cancer is responsible for 7.6 million deaths worldwide annually of which two thirds occur in low-middle income countries.

"The World Health Organisation has reported a cancer age standardised mortality rate of 122 per 100,000 population, for both sexes reported in 2004, whilst the International Atomic Energy Agency highlighted that, Zimbabwe sees, on average, 7,000 new cancer cases each year. Only a fraction of these-some 1,300 to 2,000 is treated with radiotherapy.

"The Zimbabwe National Cancer Registry 2005 report indicated that 60 percent of cancers recorded in Zimbabwe were HIV related," he said.

Dr Mombeshora said according to a study published in the International Journal of Cancer, cancer patients in Harare are not likely to survive five years after diagnosis at present levels of care.

He said the WHO projects that without immediate action the global number of deaths from cancer will increase by nearly 80 percent by 2030. Dr Mombeshora said millions of cancer deaths globally could be prevented through proven prevention, early detection and treatment approaches.

"The medicines, technologies and services are not widely available in Zimbabwe due to high cost, resulting in a lot of premature deaths each year.

"About 40 percent of some cancers can be prevented by adopting healthy life styles such as healthy diets (increased intake of fruits and vegetables), avoiding tobacco use (smoking, chewing, and snuff), and reducing or avoiding alcohol assumption.

Screening which includes Pap Smears, PSAs and Clinical Breast Examinations as well as counselling services must be made available at health centre level as part of the Non Communicable Disease prevention and control programme,” he said.

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NYTimes, September 16, 2011, 5:46 pm

**New AIDS Cases Dropped 25% This Year, City Reports**
By Anemona Hartocollis

In a sign of progress against one of the great plagues of the last generation, a dwindling number of New Yorkers have been diagnosed with AIDS over the last eight years, according to new statistics released Friday.

The number of adults newly diagnosed with AIDS dropped to 2,225 in the 2011 fiscal year, which ended June 30. That total was 25 percent lower than the total the year before (2,969 cases diagnosed), and 47 percent lower than in the 2003 fiscal year, when there were 4,164 new cases, according to the Mayor’s Management Report, which was released Friday.

Dr. Monica Sweeney, assistant commissioner of the Bureau of H.I.V. Prevention and Control in the city’s Department of Health and Mental Hygiene, said the decline was a “proxy for improved care.”

“It’s not that people are not infected” with H.I.V., the virus that causes AIDS, she said. “It is that they are taking medications, they’re able to be more adherent, treatment has become easier.”
But she added that the number of people newly diagnosed with H.I.V. has also been going down, though those numbers were not included in the report.

She said that the improving numbers had raised concerns among public health officials that the public might become cavalier in their behavior. “Many people who are not infected have what we call treatment optimism,” Dr. Sweeney said. “Why bother using a condom? Why bother not having multiple partners? — and people are still getting infected — because of the success of the treatment,” Dr. Sweeney said.

New infections were most common among men under 30, especially black and Latino men, who have sex with men; black women; and to a lesser extent Latino women, she said.

On the other hand, she said, because of programs directed at pregnant women and drug users, it is rare for babies to be born infected, and “people getting infected from intravenous drug use has gone from the thousands to 185” in 2009, the last year of complete data available.

The historic numbers tell a striking tale of an epidemic that crested and then began to fall as the means of transmission became better understood and drug treatment was simplified from a handful of pills to a single capsule containing three medications.

City charts show 52 new diagnoses of AIDS before 1981, rising to 160 in 1981, 540 in 1982, 1,097 in 1983 and then soaring to a peak of 12,745 in 1993 before beginning a gradual decline to the present levels.

In another positive statistic, deaths from unintentional drug overdoses were down to 549 in the 2011 fiscal year from 905 in 2003.

But Daliah Heller, an assistant health commissioner for alcohol and drug use prevention and care, said that the decline in deaths from traditional drugs like heroin, cocaine and methadone masked a rise in deaths from prescription opioids like oxycodone and hydrocodone.

Oxycodone is known by brand names like Oxycontin and Percocet and hydrocodone is sold as Vicodin.

She said that while public health officials had become more successful in reaching traditional addicts, they were trying to develop new strategies to reach prescription drug abusers.

“It is important that we look upstream to sources of prescription opioids — to doctors and pharmacies — because it is a preventable cause of death,” Dr. Heller said.

Scientists disarm HIV in step towards vaccine
Researchers have found a way to prevent HIV from damaging the immune system, in a new lab-based study published in the journal Blood. The research, led by scientists at Imperial College London and Johns Hopkins University, could have important implications for the development of HIV vaccines.

HIV/AIDS is the third biggest cause of death in low income countries, killing around 1.8 million people a year worldwide. An estimated 2.6 million people became infected with HIV in 2009.

The research shows that HIV is unable to damage the immune system if cholesterol is removed from the virus's membrane. Usually, when a person becomes infected, the body's innate immune response provides an immediate defence. However, some researchers believe that HIV causes the innate immune system to overreact and that this weakens the immune system’s next line of defence, known as the adaptive immune response.

In the new study, the researchers removed cholesterol from the membrane surrounding the virus and found that this stopped HIV from triggering the innate immune response. This led to a stronger adaptive response, orchestrated by immune cells called T cells. These results support the idea that HIV overstimulates the innate response and that this weakens the immune system.

Dr Adriano Boasso, first author of the study, from Imperial College London, said: "HIV is very sneaky. It evades the host's defences by triggering overblown responses that damage the immune system. It's like revving your car in first gear for too long. Eventually the engine blows out.

"This may be one reason why developing a vaccine has proven so difficult. Most vaccines prime the adaptive response to recognise the invader, but it's hard for this to work if the virus triggers other mechanisms that weaken the adaptive response."

HIV takes its membrane from the cell that it infects. This membrane contains cholesterol, which helps to keep it fluid. The fluidity of the membrane enables the virus to interact with particular types of cell. Cholesterol in the cell membrane is not connected to cholesterol in the blood, which is a risk factor for heart disease but is not linked to HIV.

Normally, a subset of immune cells called plasmacytoid dendritic cells (pDCs) recognise HIV quickly and react by producing signalling molecules called interferons. These signals activate various processes which are initially helpful, but which damage the immune system if switched on for too long.
In collaboration with researchers at Johns Hopkins University, the University of Milan and Innsbruck University, Dr Boasso's group at Imperial have discovered that if cholesterol is removed from HIV's envelope, it can no longer activate pDCs. As a consequence, T cells, which orchestrate the adaptive response, can fight the virus more effectively.

The researchers removed cholesterol using varying concentrations of beta-cyclodextrin (bCD), a derivative of starch that binds cholesterol. Using high levels of bCD they produced a virus with a large hole in its envelope. This permeabilised virus was not infectious and could not activate pDCs, but was still recognised by T cells. Dr Boasso and his colleagues are now looking to investigate whether this inactivated virus could be developed into a vaccine.

"It's like an army that has lost its weapons but still has flags, so another army can recognise it and attack it," he said.


Breast Milk Antibody Fights HIV but Needs Boost, Study Finds

ScienceDaily (Sep. 19, 2011) — Breast milk antibody both neutralizes human immunodeficiency virus (HIV) and kills HIV-infected cells, according to a paper in the September 2011 issue of the Journal of Virology.

"This finding indicates that enhancement of these responses through vaccination could help reduce HIV transmission via breastfeeding," says corresponding author Sallie Permar of Duke University, Durham, NC. While HIV-specific antibodies have been identified in breast milk, this is the first study to investigate the virus-blocking functions of these antibodies.

Nonetheless, the statistics indicate that breast milk antibodies are doing an incomplete job of protecting babies from HIV transmission. Nearly half of the 350,000 new infant HIV infections occurring annually are transmitted via breast milk. Permar’s study provides perspective: it shows that the magnitude of anti-HIV responses in breast milk is low compared to those in plasma.

Thus, the need to enhance that response. Fortunately, the study’s results suggest that current systemic HIV vaccine candidates may be effective in enhancing anti-HIV functions of breast milk antibody, and reducing postnatal HIV transmission. Permar et al. found that breast milk antibody’s activity against HIV and HIV-infected cells is mediated by IgG antibodies that originate in the blood stream, rather than IgA antibodies, which are produced in the mammary gland.

The alternative to immunologic intervention, formula feeding, "is not a viable option for reducing this mode of transmission in resource poor areas with high HIV prevalence, as it is associated with high infant mortality from diarrhea and respiratory illnesses," says Permar. "While maternal and/or infant antiretroviral prophylaxis during the period of breastfeeding is effective in reducing infant transmission, HIV transmission continues to occur in the setting of optimal prophylaxis and the effects of this long-term prophylaxis on infant growth and development are not known. Moreover, long-term prophylaxis is a challenge for resource poor areas." But a maternal or infant vaccine would be ideal for eliminating postnatal HIV transmission, she says.

Journal Reference:
Scientists have deciphered the genome of a bacterium implicated as a key player in regulating the immune system of mice. The genomic analysis provides the first glimpse of its unusually sparse genetic blueprint and offers hints about how it may activate a powerful immune response that protects mice from infection but also spurs harmful inflammation.

The researchers, led by Dan Littman, the Helen L. and Martin S. Kimmel Professor of Molecular Immunology at NYU School of Medicine and a Howard Hughes Medical Institute Investigator, and Ivaylo Ivanov, PhD, of Columbia University Medical Center, published their findings in the September 15, 2011, issue of *Cell Host and Microbe*. The study suggests that the gut-dwelling microorganism, named segmented filamentous bacteria (SFB), is genetically distinct from all 1,200 bacterial genomes studied so far, reflecting its relatively unique role in the gut.

Although SFB was first identified more than 40 years ago, it wasn't until 2009 that Dr. Littman and an international team of collaborators discovered that it can recruit specialized T cells, called Th17 cells, in the small intestine of mice. These potent immune cells, they subsequently found, protected the mice from disease-causing Citrobacter rodentium bacteria, but also made them more susceptible to inflammation and autoimmune arthritis. Those initial results suggested other intestinal bacteria might also regulate immune function.

"What has become clear in the last couple of years is that individual bacteria can specifically influence particular branches of the immune system," says Dr. Littman. In the new study, his team deciphered SFB's 1.57 million letters of DNA, almost 2,000 times smaller than our own genome and about one-third the size of its closest relative.

The microbe's sparse genome lacks many genes needed for its own survival, such as ones for making amino acids and other essential nutrients. As a result, it is dependent on other gut-dwelling bacteria or its host for food, according to the study. The examination of its 1,500 genes, however, suggests it is well adapted to the small intestine, where it clings to the thin lining and may help prevent other microbes from breaching the barrier.

Although the study didn't uncover any definitive signs of the SFB living within us, Dr. Littman suspects the resourceful bacteria have adapted to certain human populations. Even if it isn't found in our intestinal tract, scientists could apply what they have learned to obtain insights into the function of similarly acting microorganisms within us.

"Maybe in humans, there is another bacterium that is different from SFB but behaves functionally in the same way," says Dr. Ivanov, who conducted the latest analysis as a postdoctoral researcher in Dr. Littman's lab.

Recently, Japanese researchers found intestinal bacteria in humans that can boost development of regulatory immune cells in mice, thereby keeping the inflammatory activity of Th17 cells in check. Dr. Littman and his NYU collaborators may have also uncovered a microbe in the intestinal tract of rheumatoid arthritis patients that alters immune function. These emerging results underscore the need to understand how the microbes living in our bodies may impact our health.
“This research brings us the potential genetic mechanisms that trigger differentiation of Th17 cells which we have long believed to have a strong role in the development of autoimmune diseases, including rheumatoid arthritis (RA), psoriatic arthritis (PsA), and Crohn’s disease,” said Steven Abramson, MD, professor, Departments of Medicine and Pathology and director of the Rheumatology Division at NYU Langone Medical Center. “With more than 50 million Americans suffering from at least one autoimmune disease, this research gives scientists and clinicians a greater ability to apply knowledge gained in the laboratory to actual clinical cases, moving it from ‘bench-to-beside’ to give patients a tremendous advantage and physicians the ability to fine-tune medications and protocols based on patient response.”

Journal Reference:

Microbiology Puzzle Solved by Online Gamers

In an experiment called CASP9, scientists were struggling to map the structure of M-PMV, a protein involved in a virus that causes a form of simian Aids. In that experiment and others, the search had been going on for more than a decade. But the solution was not found by a laboratory but the players of an online puzzle game.

Foldit takes the best known models of proteins and offers them to game players, many of whom have no background in science at all. Armed with a set of tools to play with the model, the aim is to produce a version that is as stable as possible, with no molecules clashing with any others and low internal energy.

To solve the puzzle it is not necessary to know what the parts of the model represent, only how they work within the game. Each protein becomes a three-dimensional brainteaser that could be purely abstract but in fact represents a particle that occurs in the real world.

Players manipulate the model within the game, stretching bonds between sheets, tucking stray molecules into free spaces and eliminating voids. They gain points by producing a stable solution and can form teams that work together, combining the successful parts of their individual solutions.

In CASP9’s case, they were initially hampered by the computer modelling that had already taken place. Trapped within the automatic analysis’s best guess, they were unable to make the radical moves that eventually led to the correct answer. Once the puzzle had been re-submitted to the gamers with a greater scope for experimentation, a group calling themselves the Foldit Contenders found the correct path within ten days. A user calling herself mimi made the final modification, but she was keen to stress that it was a collective effort.

She told MSNBC: ‘I had looked at the structure of the options we were presented with and identified that it would be better if the ‘flap’ could be made to sit closer to the body of the protein – one of the basic rules of folding is to make the protein as compact as possible – but when I tried this with my solo solution, I couldn’t get it to work. However, when I applied the same approach to the evolved solution that had
been worked on by other team members, I was able to get it to tuck in, and that proved to be the answer to the structure. I believe that it was the changes made by my colleagues that enabled mine to work, so it was very much a team effort.’

The paper announcing the solving of the protein in the journal Nature Structural and Molecular Biology credits Foldit Contenders Group rather than individual players and mimi has asked that only her Foldit name should be used in press reports.

X-ray crystallography was used to confirm the solution. It is hoped that the new understanding of the protein can now be used in the design of anti-retroviral treatments, including anti-HIV drugs.

Polio strain spreads to China from Pakistan

Polio has spread to China for the first time since 1999 after being imported from Pakistan, the World Health Organization (WHO) has confirmed.

It said a strain of polio (WPV1) found in China was genetically linked with the type now circulating in Pakistan.

At least seven cases have now been confirmed in China's western Xinjiang province, which borders Pakistan.

The WHO warned there was a high risk of the crippling virus spreading further during Muslim pilgrimages to Mecca.

Polio (also called poliomyelitis) is highly infectious and affects the nervous system, sometimes resulting in paralysis.

It is transmitted through contaminated food, drinking water and faeces.

'Right things done'

On Tuesday, the WHO said the polio cases in Xinjiang had been detected in the past two months. The Chinese authorities are now investigating the cases, and a mass vaccination campaign has been launched in the region.

"So far all the right things are being done," WHO spokesman Oliver Rosenbauer told Reuters news agency.

Polio was last brought into China from India in 1999. China's last indigenous case was in 1994.

Pakistan is one of a handful of countries where polio remains endemic.

WHO officials had been warning for some time that the virus was spreading within the country to previously uninfected areas.

The UN’s children fund, Unicef, has said that eradicating polio from Pakistan depends on delivering oral vaccines to each and every child, including the most vulnerable and the hardest to reach.

Polio was virtually eliminated from the Western hemisphere in the 20th Century.

Scientists find way to "disarm" AIDS virus

Mon, Sep 19 2011

By Kate Kelland

LONDON (Reuters)—Scientists have found a way to prevent HIV from damaging the immune system and say their discovery may offer a new approach to developing a vaccine against AIDS.

Researchers from the United States and Europe working in laboratories on the human immunodeficiency virus (HIV) found it is unable to damage the immune system if cholesterol is removed from the virus's membrane.

"It's like an army that has lost its weapons but still has flags, so another army can recognize it and attack it," said Adriano Boasso of Imperial College London, who led the study.

The team now plans to investigate how to use this way of inactivating the virus and possibly develop it into a vaccine.

Usually when a person becomes infected with HIV, the body's innate immune response puts up an immediate defense. But some researchers believe HIV causes the innate immune system to overreact. This weakens the immune system's next line of defense, known as the adaptive immune response.

For this study—published on Monday in the journal Blood—Boasso's team removed cholesterol from the membrane around the virus and found that this stopped HIV from triggering the innate immune response. This in turn led to a stronger adaptive response, orchestrated by a type of immune cells called T cells.

AIDS kills around 1.8 million people a year worldwide. An estimated 2.6 million people caught HIV in 2009, and 33.3 million people are living with the virus.
Major producers of current HIV drugs include Gilead Bristol Myers Squibb, Merck, Pfizer and GlaxoSmithKline.

Scientists from companies, non-profits and governments around the world have been trying for many years to make a vaccine against HIV but have so far had only limited success.

A 2009 study in Thailand involving 16,000 volunteers showed for the first time that a vaccine could prevent HIV infection in a small number of people, but since the efficacy was only around 30 percent researchers were forced back to the drawing board.

An American team working on an experimental HIV vaccine said in May that it helped monkeys with a form of the AIDS virus control the infection for more than a year, suggesting it may lead to a vaccine for people.

HIV is spread in many ways—during sex, on needles shared by drug users, in breast milk and in blood—so there is no single easy way to prevent infection. The virus also mutates quickly and can hide from the immune system, and attacks the very cells sent to battle it.

"HIV is very sneaky," Boasso said in a statement. "It evades the host’s defenses by triggering overblown responses that damage the immune system. It's like revving your car in first gear for too long—eventually the engine blows out.

He said this may be why developing a vaccine has proven so tricky. "Most vaccines prime the adaptive response to recognize the invader, but it's hard for this to work if the virus triggers other mechanisms that weaken the adaptive response."

HIV takes its membrane from the cell that it infects, the researchers explained in their study. This membrane contains cholesterol, which helps keep it fluid and enables it to interact with particular types of cell.

Normally, a subset of immune cells called plasmacytoid dendritic cells (pDCs) recognize HIV quickly and react by producing signaling molecules called interferons. These signals activate various processes which are initially helpful, but which damage the immune system if switched on for too long.

Working with scientists Johns Hopkins University, the University of Milan and Innsbruck University, Boasso's team found that if cholesterol is removed from HIV's envelope, it can no longer activate pDCs. As a result, T cells, which orchestrate the adaptive response, can fight the virus more effectively.

**Battle of commercial interests confound fight against noncommunicable diseases**

By [David Brown](#), Published: September 20

NEW YORK — Behind two days of talks at the United Nations and a unanimously adopted [13-page document about the need to fight noncommunicable diseases](#) around the world is a fierce struggle between commercial and health interests that has only just begun.

Some of the issues, and some of the partisans, are the same ones at the heart of two other huge health campaigns in the past 20 years — the battle against smoking and the effort to bring AIDS drugs to poor countries. But the stakes are here much bigger, given the number of lives and sums of money at play.

That’s because noncommunicable diseases — heart disease, stroke, cancer, diabetes and emphysema — are deeply entangled with important global industries, not only tobacco but also food, pharmaceuticals, advertising, transportation and construction. And they are the globe’s biggest health problem, responsible for 63 percent of all deaths each year, with incidence growing steeply in the low-income, rapidly urbanizing nations of the world.

At issue are two questions: Will assaulting obesity-driven ailments require attacking the food companies the way assailing tobacco companies has driven efforts against smoking? What is the responsibility of rich countries, and the pharmaceutical companies located in them, to improve medical care in poor countries, where 40 percent of deaths from noncommunicable diseases occur before age 60?

The food industry, which is responsible for much of the sweet, salty, high-fat food that experts view as a problem, for the moment is considered a “partner” in the new campaign. It will not be treated as a pariah industry like tobacco, whose companies are barred from meetings like this.

The 13-page “Political Declaration” under intense negotiation since June and adopted Monday contains more than a dozen “partner” references. It telegraphs a message that voluntary changes in salt, fat and calories in food and in marketing directed at children are the preferred route to slowing the rise in obesity, hypertension, high cholesterol and inactivity that underlies many of the diseases.

**Activists hungry for more**

It is a position that has left many activists unsatisfied.
“Our position is that partnership isn’t the right word. It implies trust and respect,” said Patti Rundall, who helped run the campaign against infant formula sales in Africa 30 years ago and today is working to limit the marketing of processed food in the developing world. “The allegiance of the food companies is to create profits. Their voluntary commitments are only good for as long as they want to keep them,” she said.

Laurent Huber, 41, a Swiss exercise physiologist who works for an anti-smoking group, said, “The fast-food industry and the junk-food industry cannot be engaged in the policy process. They are part of the problem. This conflict of interest needs to be looked at.”

Nevertheless, many companies have agreed to slowly reduce salt in processed food, remove trans fats and remake restaurant dishes so they contain less fat. This month, the company that owns the Red Lobster and Olive Garden restaurants promised to take that last step.

The bigger issue in preparing the document, however, was how much to invoke the international trade agreements that indirectly have helped bring life-saving antiretroviral drugs to nearly 7 million people with HIV infection in low-income countries in the last decade.

In 2001, the World Trade Organization’s agreement on intellectual property, known informally as TRIPS, was amended in Doha, Qatar, to help developing nations gain access to AIDS drugs. The Doha Declaration said a poor country could force pharmaceutical companies to let manufacturers make generic drugs for use in low-income countries, in exchange for a small royalty.

This option helped persuade U.S and European drug companies to voluntarily let offshore companies make versions of their high-priced drugs long before the patents expired. This prevented “compulsory licensing,” as the Doha mechanism is called, from becoming common practice.

The Doha Declaration referenced HIV, tuberculosis, malaria “and other epidemics.” Whether that might cover “epidemics” of noncontagious diseases such as diabetes and hypertension wasn’t mentioned — or probably even considered.

The document from this week’s U.N. meeting doesn’t mention the Doha Declaration, although it does mention “full use of TRIPS flexibilities.” It also doesn’t describe the noncommunicable diseases as epidemics; it calls them “a challenge of epidemic proportions.”

Many experts and activists interpret these omissions as evidence that rich countries don’t want their drug companies to be pressured into repricing cancer and heart medicines for the developing world as they were for antiretrovirals. There are far more drugs for noncommunicable diseases; many are pricier than AIDS drugs; and there are hundreds of millions more patients who could use them.

“We really believe that Doha was not meant to be so narrowly interpreted, that it was intended to address all public health crises,” said Krista L. Cox, a lawyer for Knowledge Ecology International, a four-person organization with offices in Washington and Geneva that campaigns for global health equity. Pharmaceutical Research and Manufacturers of America takes a different view.

“Compulsory licenses are intended to be used to address health emergencies and to provide urgent access in situations where there is little or no availability of existing effective medicines,” said Jay Taylor a vice president of the trade group. “This situation is clearly not the case in the context of the growing burden of noncommunicable diseases … there are hundreds of low cost generic medicines to treat NCDs in low-income countries that simply are not getting into the clinics and pharmacies or into the hands of the patients that need them most.”

The organization’s member companies would work to provide those to needy countries, he said.

A summary of the negotiations, made available to The Washington Post on the condition it not be quoted directly, shows that U.S. negotiators at one point threatened to scuttle the document if it mentioned either TRIPS or Doha. A compromise was reached in which the former was included but not the latter, and also no reference to “epidemics.” This was viewed as giving future negotiators more flexibility in issues of compulsory licensing.

A U.S. government official familiar with the talks had a different account. The official said there was little debate over a Doha reference and that its absence from the final document is insignificant because Doha is part of TRIPS. As for “epidemics,” the official said, negotiators simply stuck to the medical definition, which requires contagion.

Asked about the Doha omission on Tuesday, the director-general of the World Health Organization, Margaret Chan, took a similar position: “Any member of the WTO can exercise the TRIPS flexibility, and that’s it.”
Advocates, Doctors Split on HIV Test Bill

*Boston Globe*, (09.20.2011) Kay Lazar

Health providers and advocates are divided over a bill intended to bring Massachusetts into compliance with CDC recommendations on making HIV testing a routine part of medical care. The bill would enable the informed consent process for HIV testing to be conducted orally and documented by the provider in medical records. Currently, the state requires written patient consent specifically for the HIV test.

However, to accommodate privacy concerns, legislators this year added a provision that would require a health care provider to obtain a patient’s written consent every time his or her HIV-related information is shared with outside providers. Some stakeholders support that requirement. Others, however, balk at the bill they once backed, saying it would hinder HIV patients’ ability to receive care in a timely fashion.

A coalition of more than 100 health care providers—including Fenway Health, the Massachusetts Medical Society, and the Massachusetts Hospital Association—is urging legislators and health officials in Gov. Deval Patrick’s administration to block the bill. The measure has passed two subcommittees and awaits a full Senate vote.

“The entire country is going in the other direction, to make information sharing easier and more thorough,” said Dr. Howard Heller, president of the Massachusetts Infectious Diseases Society. “This is a step backward.”

The bill’s supporters say such safeguards remain necessary to protect patients’ privacy. “HIV is still stigmatized, and many people fear the disclosure of HIV status,” said Ben Klein, AIDS law project director at Gay & Lesbian Advocates & Defenders. Other backers of the measure include the American Civil Liberties Union of Massachusetts and the nonprofit AIDS Action Committee of Massachusetts.

Rebecca Haag, president and CEO of AIDS Action, noted her support of the bill’s provision requiring health care providers to document that they offered HIV testing to a patient.

Religiosity as a Protective Factor Against HIV Risk Among Young Transgender Women

*Journal of Adolescent Health Vol. 48; No. 4: P. 410-414*, (04..2011) Nadia Dowshen, MD; Christine M. Forke, MSN, RN, CRNP; Amy K. Johnson, MSW; Lisa M. Kuhns, PhD, MPH; David Rubin, MD, MSCE; Robert Garofalo, MD, MPH

“Young transgender women (YTW) face many challenges to their well-being, including homelessness, joblessness, victimization, and alarming rates of HIV infection,” explained the study authors. Noting a dearth of literature on potential HIV prevention factors in this population, the researchers aimed to examine the role of religion in YTW's lives and its relationship to HIV risk.

Using baseline data collected for an HIV prevention intervention, the study incorporated a convenience sample of YTW ages 16-25 from Chicago who were recruited consecutively and completed an audio computer-assisted self-interview. Logistic regression models were used to evaluate the relationship between sexual risk-taking (sex work, multiple anal sex partners, unprotected receptive anal sex), alcohol use, formal religious practices (service attendance, reading/studying scripture), and God Consciousness (prayer, thoughts about God).

Ninety-two YTW participated in the study; mean age was 20.4 years; 58 percent were African-American, 21 percent white and 22 percent other. Multivariate logistic regression showed alcohol use was significantly associated with sexual risk in both models, with adjusted odds ratio of 5.28 (95 percent confidence interval: 1.96-14.26) in the Formal Practices model and 3.70 (95 percent CI: 1.53-8.95) in the God Consciousness model. After controlling for alcohol use, the Formal Practices model was found to be significantly associated with sexual risk (OR=.29, 95 percent CI:.11-.77) while God Consciousness was not (OR=.60, 95 percent CI:.25-1.47).

“Among YTW, formal religious practices may attenuate sexual risk-taking behaviors and therefore HIV risk. Further research is needed to explore the role of the religion in the lives of YTW as a protective asset,” the study authors concluded.

Rogaine as Possible HIV Cure?

*Albuquerque Journal*, (08.13.2011) Olivier Uyttebrouck

The quest for low-cost HIV treatment may lie in finding virus-fighting properties among the thousands of drugs already approved by the Food and Drug Administration, according to Vojo Deretic, chair of molecular genetics and microbiology department at the University of New Mexico.
Deretic’s team has received a $1 million grant from the Bill & Melinda Gates Foundation to study existing drugs that could increase a cell’s ability to combat HIV. The researchers are focused on a cellular process called autophagy, or Greek for “self-eating,” in which cells produce specialized cellular subunits, called autophagosomes, that remove unwanted material. Thousands of drugs will be examined in search of compounds that encourage cells to produce autophagosomes in large numbers, said Deretic.

Central to the task is a screening device that produces high-resolution photographs of the cell interiors. A state-of-the-art computer program will “look inside the cell and see structures and quantify them,” Deretic explained.

Rogaine, a hair regrowth treatment, is among the medicines showing early promise, said Deretic. Others include albuterol, a fast-acting asthma drug, and lithium, which is used to treat depression and bipolar disorder.

Later in the two-year study, the team will test combinations of the most promising drugs. “My feeling is it’s going to take two [drugs] in a combination,” said Deretic. “We want to find the cheap drug, relative to what a new drug would cost, and see if it can do the trick,” Deretic said.

ICAAC: Zinc Finger Gene Therapy Boosts CD4 Cells, May Lower HIV Viral Load
Published on Monday, 19 September 2011 00:00
Written by Liz Highleyman
© Russell Kightley

HIV positive people who had their CD4 T-cells altered to delete the CCR5 coreceptor continue to experience sustained CD4 cell increases, and a subset of participants with high levels of modified cells maintained lower viral load during an investigational treatment interruption, researchers reported at the 51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC 2011).

Despite the availability of effective antiretroviral therapy (ART), a cure for HIV remains the holy grail of research. The case of the "Berlin Patient"—a man who apparently remains free of HIV 5 years after receiving a bone marrow transplant for leukemia from a donor naturally lacking CCR5—offered proof-of-concept that a functional cure is possible.

Most strains of HIV use the CCR5 coreceptor, along with the CD4 receptor on the surface of certain T-cells, to enter cells and establish infection. A small percentage of people (about 1% of Northern Europeans) who have a natural genetic variation known as CCR5-delta-32 do not express this coreceptor on their cells, and are therefore protected against HIV infection.

Researchers are studying gene therapy technology that uses a zinc finger nuclease (ZFN) developed by Sangamo BioSciences to cut the CCR5 gene out of CD4 cells, in the hope of making them resistant to HIV, like cells that naturally lack the coreceptor.

Study participants have some of their CD4 T-cells removed and treated with the ZFN. The altered cells—known as SB-728-T—are multiplied in a laboratory and infused back into the same patient.

At the Conference on Retroviruses and Opportunistic Infections (CROI) this past March, researchers presented the first data from the Phase 1 study. As reported by study participant Matt Sharp, modified T-cells multiplied in the body and migrated to the gut like normal cells. In addition, most participants experienced sustained CD4 cell increases.

At ICAAC, Ronald Mitsuyasu from UCLA presented further data from 9 participants in the West Coast branch of study who at baseline had suboptimal CD4 cell recovery (< 500 cells/mm³; median 384 cells/mm³) despite undetectable viral load on ART. All were men, the median age was about 50 years, and they had been HIV positive for a median of about 20 years.

Results

- SB-728-T modified CD4 cells persisted for a median of 337 days, with a maximum of 561 days.
- Modified T-cells continued to multiply in the body and migrate or "traffic" to the rectal mucosa like normal cells.
- About 25% of patients’ CD4 T-cells showed the CCR5 deletion.
- All participants had sustained CD4 cell increases (median gain of 163 cells/mm³).
- Most also had improved CD4/CD8 T-cell ratios.
- The treatment continued to be well-tolerated, with no unexpected adverse side effects.
- A majority of adverse events were transient injection site reactions and flu-like symptoms during the first 24 hours following infusion of modified cells.
In a late breaker session Dale Ando from Sangamo reported data from the East Coast branch of the study, run by Carl June and Pablo Tebas of the University of Pennsylvania. In this protocol, 6 participants with CD4 counts > 450 cells/mm$^3$ underwent a 12-week analytic ART interruption starting 4 weeks after receiving SB-728-T modified CD4 cells.

**Results**

- Higher levels of circulating modified T-cells with both copies of the CCR5 gene deleted were significantly associated with lower viral load during treatment interruption.
- 3 of 6 participants with the highest levels of T-cells with the double or biallelic CCR5 deletion experienced viral load declines of 0.8 to >2.0 log during ART interruption.
- One participant who was CCR5-delta-32 heterozygous—meaning he had 1 gene copy with the natural CCR5 deletion and 1 normal CCR5 gene—achieved undetectable viral load during treatment interruption after receiving SB-728-T modified cells.

"The data obtained in our treatment interruption studies are very exciting and represent significant progress toward a 'functional cure' for HIV/AIDS," June said in a press release issued by Sangamo.

9/20/11

**References**


**Certain Heavy Metals Boost Immunity, Study Suggests**

ScienceDaily (Sep. 20, 2011) — A new natural defense mechanism against infections has been evidenced by an international team led by researchers from CNRS, Inserm, the Institut Pasteur and the Université Paul Sabatier—Toulouse III[1]. Zinc, a heavy metal that is toxic at high doses, is used by the cells of the immune system to destroy microbes such as the tuberculosis bacillus or E. coli.

Published in the journal *Cell Host & Microbe* on 14 September 2011, this discovery makes it possible to envisage new therapeutic strategies and test new vaccine candidates. One of the well-known strategies employed by our immune system to destroy microbes consists in depriving them of essential nutrients such as heavy metals, particularly iron. For the first time, an international study headed by researchers from the Institut de Pharmacologie et de Biologie Structurale (CNRS/Université Paul Sabatier—Toulouse III), the Centre d’Immunologie de Marseille Luminy (CNRS/Inserm/Université de la Méditerranée) and the Institut Pasteur has shown that the reverse is also true: the immune cells are capable of mobilizing reserves of heavy metals, especially zinc, to poison microbes.

This phenomenon has been demonstrated for *Mycobacterium tuberculosis*, the agent responsible for tuberculosis in humans, which accounts for nearly 2 million deaths worldwide each year, and for *Escherichia coli*, of which certain strains can cause serious infections of the digestive and urinary systems. In immune system cells (macrophages) that have ingested *M. tuberculosis* or *E. coli*, the researchers observed a rapid and persistent accumulation of zinc.

They also observed the production, on the surface of the microbes, of numerous proteins whose role is to "pump out," in other words eliminate, heavy metals. In macrophages, the microbes are thus exposed to...
potentially toxic quantities of zinc and they try to protect themselves against intoxication by synthesizing these pumps. Inhibiting the pumps through genetic engineering provides proof of evidence: *M. tuberculosis* and *E. coli* become even more sensitive to destruction by macrophages.

Zinc, although toxic when ingested in too high quantities, is therefore beneficial for the immune system, particularly because it is used by macrophages to poison microbes. Equivalent mechanisms could exist for other heavy metals such as copper. These results have very concrete clinical implications. In particular, they re-open the debate on dietary supplementation (e.g. with zinc) and they may also lead to new antibiotics that would block the action of microbial pumps on metals or to new attenuated vaccine strains, which have already been tested as vaccine candidates.

**Journal Reference:**

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**Could Engineered Fatty Particles Help Prevent AIDS? Liposomes Block HIV Infection in Early Tests**

ScienceDaily (Sep. 21, 2011) — Could engineered fatty particles help prevent AIDS? Liposomes block HIV infection in early tests; could be a cost-effective preventive for developing countries

HIV vaccines are in their infancy, and effective microbicides to prevent sexual transmission of HIV still don't exist. Protection is especially needed for women, who make up nearly half of all global cases. Researchers at Children's Hospital Boston envision a new way for women to protect themselves before sex: an applicator filled with specially formulated fatty particles called liposomes.

In tests led by Daniel Kohane, MD, PhD, director of the Laboratory for Biomaterials and Drug Delivery at Children's Hospital Boston, liposomes inhibited HIV infection in cell culture and appeared safe in female mice when injected intravaginally. The findings are reported in the November issue of the journal *Biomaterials*, published online Sept. 19.

Liposomes are spherical particles with a double outer layer of lipids (fats) and hollow centers. They are relatively easy and cheap to engineer, and thus present a viable option for developing countries, where the cost of anti-HIV drugs bars access for most people.

Liposomes can be filled with drugs or other compounds, but in this case, Kohane and colleagues found, to their surprise, that the liposomes alone were effective in blocking infection.

"We had been planning do much more complex things, like putting ligands on the surface to increase binding to HIV," says Kohane. "It was a surprise that liposomes alone worked so well. Simplicity is always better—if liposomes work by themselves, we may not need anything else, and it would be cheaper and potentially much safer."

Kohane and colleagues hope to conduct further tests to better understand how the liposomes are blocking infection. They bind to HIV, perhaps interfering with the virus's ability to fuse with cell membranes, the first step in infection.

"The idea, simplistically, is that liposomes look like cell membranes," says Kohane, "so maybe we could use them as decoys to prevent HIV infection."

Kohane and colleagues formulated a range of liposomes using various naturally occurring and synthetic lipids and screened them systematically in cell cultures. Several formulations showed a good therapeutic profile, protecting the cells from HIV infection without being toxic. Especially effective were liposomes containing cardiolipin, a fat that was first found in animal hearts; performance was further improved by adding a synthetic phospholipid.

Tested in female mice, these formulations caused little or no inflammation, which can compromise the vaginal lining and increase the risk of HIV transmission. Imaging confirmed that the liposomes remained in place or left the body, but did not travel beyond the vagina.

"This research makes an important contribution towards creating a safe and effective form of HIV prevention for women," says Nikita Malavia, PhD, the study's first author, who worked in Kohane's lab and in the lab of Robert Langer, ScD, of MIT. "Women in areas such as sub-Saharan Africa often cannot control their male partners' use of condoms, making them three times more likely to be HIV-positive than men. This technology could enable women to take control in their own hands."
Though some intravaginal compounds are in the pipeline, none are available yet. The advantage of using liposomes is that they are inexpensive, easy to formulate into ointments or gels, and stable for long periods of time, making them a particularly good option in resource-poor settings.

Kohane hopes to get further funding to test liposome formulations in other animal models.

**Journal Reference:**

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**Blood Simple**

A veterinary vaccine spawned products that could clean the HIV virus from blood supplies.

*By Tia Ghose | August 31, 2011*

Laurence Corash hoped that a plant extract used to make a veterinary vaccine could help prevent HIV infection in his hemophilia patients. Cerus Corporation

Laurence Corash, a hematologist at the University of California, San Francisco, started hearing reports in the early 1980s that demand for the antibiotic pentamidine was skyrocketing. The drug was used to treat pneumocystosis, a severe pneumonia caused by a yeast-like fungus that typically gained a foothold by exploiting the weakened immune systems of very old or severely malnourished people.

Some of Corash’s hemophilia patients, who were otherwise healthy, started contracting the fungal disease and taking pentamidine to combat the infection. Searching for a cause for this trend, Corash realized that his patients had one thing in common: they were getting injections of a concentrated blood extract called factor VIII to help their blood clot. It dawned upon the physician that something in the factor VIII preparations might be destroying his patients’ immune systems.

By 1984, Corash realized that the newly characterized HIV virus was the causative agent. “It was a very sad and gut-wrenching experience to have to sit down with people and say, ‘You got this disease from the products I gave you, and I don’t have a treatment for you,’” Corash says. “To see 300 people get HIV infections from the treatments that you give them is a very disturbing thing.”

So when researchers at Advanced Genetics Research Institute (AGRI), a Berkeley, California, veterinary pharmaceutical company, called Corash to help them run routine blood tests on a new vaccine against the feline leukemia virus, he wondered whether the agent used to inactivate the virus for the vaccine, a defensive chemical produced by plants called a psoralen, might also inactivate HIV, and so protect his hemophilia patients from acquiring the disease from factor VIII preparations. The AGRI scientists realized that psoralens, which prevented DNA and RNA replication in most viruses and bacteria, could conceivably wipe out any pathogens in blood products like factor VIII without harming the patient, because the plasma from which factor VIII is derived does not contain any cells or nuclei to be damaged by the treatment.

The vaccine’s virus-inactivating agent, a chemical called 8-methoxypsoralen, normally drifts harmlessly in and out of cells and nestles inside nucleic acid helices. But when the psoralen molecule is hit with UV light, two photons bind the ends of the molecule, one to each strand of the DNA, and “tie the strands together,” preventing replication, says John Hearst, a founder of AGRI and a molecular biologist at the University of California, Berkeley, who studied some of the first synthetic psoralen compounds in the 1970s. Carl Hanson, who was then a postdoctoral student in Hearst’s lab, discovered that the cross-linking worked in both RNA and DNA, and reasoned that it could thus prevent bacteria, viruses, and eukaryotic cells from replicating.

“Using drugs that target DNA and RNA was very innovative as a concept,” says Richard Benjamin, chief medical officer for the American Red Cross. Several members of Hearst’s lab began meeting for coffee at Oliveto Restaurant near Berkeley to brainstorm ways of using psoralens to develop blood-cleaning products, says Hanson, who is now at the California Department of Public Health.

To show that the approach could actually prevent the transmission of disease, Corash and collaborator Harvey Alter of the National Institutes of Health mixed concentrated factor VIII preparations with hepatitis B and C viruses, added psoralens, and then shone UV light on the preparations. Healthy chimpanzees transfused with the treated factor VIII and other psoralen-cleaned concentrates were disease-free months later.

The group formed a startup called Steritech and began synthesizing psoralen compounds that could inactivate viruses and bacteria more quickly. Their original product took 8 hours to clean a few hundred milliliters of blood; by the end of 1993, newer variants could clean the same amount of blood in less than 3 minutes.
Steritech (renamed Cerus in 1997) would go on to develop pathogen-inactivation products to scrub red blood cells, plasma, and platelets of HIV and several other viruses and bacteria. The technology is currently used in parts of Europe and Asia to clean blood supplies of dozens of pathogens such as SARS, MRSA, and HIV, and is currently under FDA regulatory review. When more than one-third of the population on the French island of Réunion in the Indian Ocean was infected with a rare arthritis-causing virus called Chikungunya, France hired Cerus to sterilize the entire blood supply on the tiny Indian Ocean outpost.

The Toll of 9/11
People exposed to the dust cloud from the World Trade Center collapse still suffer from health problems.
By Tia Ghose | September 11, 2011

Ten years after the twin towers collapsed, firefighters, construction workers, and people who lived in lower Manhattan continue to face a number of health problems, due largely to exposure to airborne particles released following the attacks on September 11, 2001.

The disaster became an unprecedented public health emergency and several state and local agencies have been keeping tabs on tens of thousands of people in Lower Manhattan who were exposed to the dust cloud.

When the towers collapsed, they released a dust cloud made of 1.2 million pounds of concrete, gypsum, molten electronics, and asbestos particles, as well as burning jet fuel, and other materials, said William Rom, a pulmonologist at New York University Langone Medical Center and Bellevue Hospital, who has studied some of the health problems of the victims. For months after the attacks, the site smoldered, releasing a hot stew of toxic volatile chemicals and carcinogens. The dust cloud reached all of Lower Manhattan and even into Brooklyn.

As a result, hundreds of thousands of people—firefighters, rescue workers, construction workers, and residents—inhaled a huge amount of chemical-laced dust, said olfactory scientist Pamela Dalton of the Monell Chemical Senses Center, who has studied the nasal function of exposed individuals. “The exposure itself was unprecedented.”

Breathing Troubles
Several different studies have noted increased rates of asthma, sinusitis, and acid reflux disease in exposed firefighters, rescue and recovery workers, and people living near Ground Zero. Rom and his colleagues analyzed the symptoms of 362 firefighters, most of whom were exposed to the site. By October 5, 2001, 80 percent of those present on the morning of the attack reported coughing, shortness of breath, chest pain, and wheezing. In the first year, lower airway lung function dropped significantly for the group, though it eventually stabilized at a lower level, he said.

The inhaled particles could have set off inflammation in the respiratory system, which likely played a large part in the symptoms people experienced, said Mayris Webber, the supervising epidemiologist for the World Trade Center Medical Monitoring and Treatment Program. “Many disorders occurring after 9/11—including asthma, bronchitis, sinusitis, and acid reflux—have been associated with chronic inflammation.”

A firefighter clears soot from his eyesU.S. Navy, Photographer’s Mate 2nd Class Jim Watson

More immediate respiratory problems stemmed from the dust cloud’s polychlorinated biphenyls, highly irritating organic compounds used in 1970’s electronics. Furthermore, because the pH of the material was so alkaline, similar to lye, the dust caused immediate shortness of breath and coughing as they got lodged in the small branches of the lungs, Rom said.

When Rom’s group looked at biopsies of the tissue, small particles can still be found deep in the lungs years later.

Mental Health Problems
Many people in NYC that fateful day were also burdened by post-traumatic stress disorder and depression. Several years later, 19 percent of the more than 70,000 people who entered the World Trade Center Registry had some symptoms of post-traumatic stress disorder, including flashbacks and trouble sleeping, compared to less than 4 percent of the overall population, said Sharon Perlman, an epidemiologist with the NYC Department of Mental Health and Hygiene who has studied the exposed populations.

Those who worked in rescue and recovery during the earliest and most intense parts of the tragedy were likelier to experience PTSD, as well as women, Hispanics, residents of the immediate area, and those
who had lower levels of support from family and friends, said James Cone, a doctor and epidemiologist with the NYC Department of Mental Health and Hygiene who also studied these populations.

Many rescue and recovery workers also faced depression, anxiety, and substance abuse, Perlman added. And those with a mental health problem are also likelier to also have symptoms such as asthma or gastrointestinal reflux disease.

**Smell Compromised**
The dust cloud also wiped out the sense of smell for many workers. When Dalton and her colleagues exposed 102 WTC workers to a rose-water like scent, “some people could smell nothing,” she said, and virtually everyone had reduced sensitivity compared to similar workers who had never been exposed.

Even more troubling, 75 percent of the people couldn’t detect an irritant, something that normally caused burning and stinging in the nose. The culprit in this case, as in the lower airways, is likely the inflammation caused by particulates, which damages the cells that contain smell receptors.

Noses also contain metabolic enzymes that convert toxic chemicals into less dangerous byproducts, but chronic inflammation can wipe out that function. So worker with impaired noses may not only be less able to detect poisonous chemicals, they may also be more vulnerable to them, Dalton said.

Losing the sense of smell also subtly affects people’s experience of life, she added. “We don’t really think our sense of smell as adding that much to our lives. But when people do lose it, it’s like everything has become sort of pastel instead of highly saturated.”

**Going forward**
One of the biggest lessons from the disaster is that consistent use of face masks can help reduce the health toll. Those who consistently and early wore disposable paper filters (like those used in hospitals), known as respirators, fared better than those who went without, Perlman said.

In the coming years, the health toll may only grow. Instead of seeing symptoms dissipate, “we’re seeing cumulative incidence rates continue to creep up over time,” said Matthew Mauer, a physician with the New York State Department of Health who is monitoring health in exposed state employees.

A study in the September 3 issue of *The Lancet* found a 19 percent uptick in cancer incidence 7 years after 9/11 among 9,853 firefighters who were exposed to the site. While it’s not clear that the cancer increase is directly caused by some exposure at Ground Zero, the link is plausible, said Webber, who was involved in the study. “Inflammation could lead to cancer because of the activities of leucocytes, including the production of proteins (cytokines and chemokines) that alter the behavior of target cells, stimulation of blood vessel growth (angiogenesis), and tissue remodeling.”

And that may just be the tip of the iceberg. Because cancer usually takes decades to develop, it’s possible that cancer rates are going to be even higher, Mauer said.

In addition, some of the respiratory problems could eventually worsen, with greater numbers of workers experiencing chronic obstructive pulmonary disease, a disease that often plagues longtime smokers, Mauer said. And as exposed populations get older, monitoring programs may start to see a higher mortality rate in the rescue workers, he added.

“We don’t know for sure what the long term implication is,” Mauer said. “That’s the million dollar question.”

**1918 Flu Spread Before Peak ***
**The 1918 influenza was circulating silently before it began killing millions of people in just a year and a half.**

*By Tia Ghose | September 19, 2011*

The “Spanish” influenza was circulating in the population months before it peaked in the fall of 1918, according to a study published today (September 19) in the *Proceedings of the National Academy of Sciences*. The earlier cases could help reveal the flu’s geographic origin and how it evolved to be so infectious.

“They’ve done a really outstanding piece of work,” said Robert Webster, a virologist at St. Jude Children’s Research Hospital, who was not involved in the study. “This virus became extremely pathogenic in young men at about the time of the end of World War I,” and in order to do so it had to evolve to be more transmissible. “This paper shows how some of the changes occurred,” he added.

The 1918 influenza, which is thought to have evolved from an avian flu, began infecting young soldiers in September of 1918 and ultimately killed roughly 50 million people worldwide, said Jeffery Taubenberger, a viral pathologist at the National Institute of Allergy and Infectious Diseases. While some theories suggest the virus spread from water fowl to pigs on farms in the Midwest United States, where it
emerged in its more deadly incarnation, no one knows for sure where the virus came from and how it became so virulent.

To find out, Taubenberger and his colleagues analyzed viral RNA from 68 autopsy samples of army recruits who had died in the months before and during the peak of the 1918 epidemic. Four of those samples came from the months of May to August, up to four months before the death toll started exploding. Consistent with later samples, early victims usually died because of pneumonia that took hold after being infected with the flu virus. The later cases didn’t seem to cause more severe disease than earlier ones.

But the researchers also found some key changes between the viruses isolated from earlier flu victims and those who died in the heat of the epidemic. Namely, in earlier cases, the hemagglutinin binding receptor, which helps the virus get a foothold in the body, was slightly more similar to that found in avian flu, while later cases showed a better fit with human hemagglutinin. Though the newer form of the receptor didn’t seem to make the disease replicate anymore quickly, “one possibility is that the form that predominates in the later fall case might have been more transmissible,” Taubenberger said. The findings also show that the flu was circulating earlier than previously documented. In addition, the study offers a snapshot of how the virus was evolving, and further analyses may reveal what caused it to be so deadly.

Understanding what made this historic scourge so deadly could aid in designing treatments for modern flu, because all the flu pandemics that have occurred since are descendants of the 1918 version, Taubenberger said.

To get a more complete picture, Webster added, “it would be wonderful if they could obtain earlier clinical material for analysis to determine the precursors a little bit more about where these viruses came from.”


**Anti-aging Pathway Questioned**

A new study raises further doubts about the ability of proteins called sirtuins to slow aging, but the controversy remains unsettled.

**By Tia Ghose | September 21, 2011**

A new study adds fuel to the fire against the notion that a class of proteins called sirtuins can prolong life. The proteins generated significant excitement when earlier studies showed they could increase lifespan in several animal species, but several groups’ inability to repeat the results raised doubts about the finding. The new study, published today (September 21) in *Nature*, provides the most convincing evidence yet against sirtuins’ role in aging.

“It’s an important paper,” said Brian Kennedy, an aging researcher and President of the Buck Institute for Research on Aging, but it is unlikely to lay the controversy to rest. “The thing we still have to understand—from yeast all the way to mice—is whether enhanced sirtuin activity expands lifespan,” said Kennedy, who was not involved in the study. “That’s really an open question right now.”

**Anti-aging pill?**

For decades, researchers have found that cutting calories can extend lifespan in species from worms to rhesus monkeys. “So one of the long-term dreams of aging was that you could have a pill that would mimic the effects of dietary restriction because it could slow human aging,” said study co-author David Gems, a biogerontologist at the University College London.

In 1995, a potential drug target emerged. When Kennedy, MIT molecular biologist Leonard Guarente, and colleagues targeted a gene which silenced sirtuins, a class of proteins that plays a role in several metabolic pathways, they increased the number of times yeast cells divide by 30 percent. In 2001, Guarente and his colleagues showed that transgenic worms that over-express a specific sirtuin called sir2 lived longer, and others showed that dietary restriction increased life span in fruit flies by way of a sirtuin pathway.

Taken together, the studies created a compelling story: cutting calories activates a sirtuin pathway, which extends lifespan in many animal species. That raised hopes that scientists could one day create a human anti-aging pill by stimulating sirtuin production directly, bypassing the need to skimp on calories. A company called Sirtris Pharmaceuticals even formed to develop anti-aging compounds that could do just that.
Doubts emerge
While some labs saw dramatic life extension with sirtuins, other groups had trouble replicating those findings. After three years without success, Gems and his colleagues began to suspect the genetic background was confounding their studies. In other words, the method for activating the sir2 gene in worms and fruit flies may have inadvertently introduced other genetic mutations that increasing longevity.

To weed out this genetic background, he and his colleagues created transgenic worms that overexpressed sir2 using the same method for gene insertion that Guarente originally used in his long-lived worms. The researchers mated the transgenic worms with wild-type animals and selected for offspring that still expressed high levels of sir2. Those worms were mated again with wild-type worms. After six generations, the resultant worms still made more sir2, but were genetically almost identical to wild type.

The outcrossed sir2 worms did not live longer than the wild-type controls, suggesting that some other gene must account for life extension in the original worms. Sure enough, a little more digging revealed another mutation in a neurodegeneration pathway that was responsible for the longevity effect. When they took a second look at flies, they found the same story: sirtuins didn’t seem to extend lifespan compared to genetically similar controls.

To see whether dietary restriction’s increased longevity depends on the sirtuin pathway, the group knocked out sir2 expression in flies and put them on a meager diet. The flies still lived longer, suggesting that sirtuins were not responsible.

Gems thinks the new findings should lay to rest the notion that sirtuins play a major role in extending lifespan across species. “Because of what a huge paradigm sirtuins created, it’s quite extraordinary that it’s sort of vanishing so suddenly,” he said. “It’s like a bubble popping.”

Continued Controversy
But not everyone in the anti-aging community is ready to abandon sirtuins. In a Brief Communications Arising published in the same issue of Nature, Guarente, who published the first studies showing dramatic life extension in worms, said they also later recognized the problem with their transgenic method. However, when they corrected for it in further experiments, they found a smaller, but still significant, 10 to 14 percent increase in lifespan in worms. The effect has since been confirmed by another lab in a study published this year in PLoS Genetics, he said.

“I do not agree with the notion that in worms, sirtuins do not regulate aging. I think that’s wrong,” Guarente said.

Stephen Helfand, a molecular biologist at Brown University who did some of the original work showing life extension in fruit flies, also took issue with the conclusions of the Gems paper. In 2009, his group confirmed that sirtuins extended life in fruit flies, using a careful method that eliminates the problem of genetic background, he said. He also faults the current paper for not replicating all the conditions used in his original experiments.

But the modest effect found in the more recent studies isn’t particularly exciting, Kennedy said. “In Lenny’s paper the effects are 10 to 14 percent,” but hundreds of genes in worms can extend lifespan by that much, he added.

Furthermore, the findings in flies and worms may not be central to the question of sirtuins and aging, Kennedy said. “Really what we care about is humans, and the best way to understand that is to have better data in mice.”
While the jury is still out on sirtuins and longevity in mammals, there’s no question that they extend health. “There’s a huge body of work that implicates sirtuins in suppression of many age-related disorders in mammals,” such as cardiac fibrosis, diabetes, obesity, neurodegeneration, and even age-related hearing loss, said David Lombard, a biogerontologist at the University of Michigan, Ann Arbor, who wrote an accompanying News and Views piece in *Nature*.

And while the debate over sirtuins’ role in aging rages on, biologists will continue to investigate other potential targets, such as the Target of Rapamycin (TOR) pathway. “It’s been shown that other pathways have very dramatic effects on aging which are not controversial and have not been challenged,” Gems said. “There’s lots of activity elsewhere in the field moving towards drug treatments for aging.”


**Again: No XMRV-Chronic Fatigue Link**

Researchers publish yet another study against the link between a murine leukemia virus and chronic fatigue syndrome, and partially retract the original results.

*By Tia Ghose | September 22, 2011*

The presence of a mouse leukemia virus is not correlated with chronic fatigue syndrome (CFS), according to a study published today (September 22) in *Science*. The study, just one of many in the last year that have discredited the relation between the two, is accompanied by a partial retraction of one of the original papers to propose such a link.

“For most of us, the final nail [in the coffin] came a long time ago!” said Myra McClure in an e-mail, an Imperial College London retrovirologist who first questioned the link between the virus and CFS, but was not involved in the new study. “However, the way this study was conducted (same samples investigated under controlled conditions in different laboratories) should convince all.”

In 2009, researchers at two labs found the presence of xenotropic murine virus-related virus (XMRV) in blood samples from patients with chronic fatigue syndrome. The findings caused a stir in the chronic fatigue community, with many sufferers wondering whether the virus caused the chronic flu-like illness.

But other researchers doubted the results and follow-up work failed to replicate the findings and two other studies traced the presence of XMRV to lab contamination. After the initial questions arose, the National Institutes of Health (NIH) funded two rigorous trials which would test blood samples in a blinded fashion at several different labs.

In the first trial, pathologist Michael Busch of the Blood Systems Research Institute in San Francisco and colleagues collected blood samples from healthy controls and chronic fatigue sufferers, including some who previously tested positive for XMRV. They then masked the origin of the samples and sent them to be tested for XMRV by nine different labs across the country, including the two labs that originally reported the positive association.

Only samples sent to the latter two labs tested positive for XMRV, and CFS patient samples were no more likely to test positive for XMRV than those of healthy controls. In addition, samples from the same patient often had contradictory test results, Busch said. “There are problems with the accuracy and specificity of their assays and their earlier results,” Busch said, although what the actual problems were remains unclear.

In the same issue of *Science*, one group that published the original paper retracted part of their results because DNA plasmids they used were contaminated with XMRV, making the idea of lab contamination as the source of XMRV ever more convincing. A full retraction of the paper is “long overdue,” McClure said.

The finding “eliminates concern that that virus is a major determinant or causative agent involved with chronic fatigue,” Busch said. These results, combined with the final NIH trial that will be completed later this year, should definitively discredit the XMRV-chronic fatigue theory, he said.

Couples often disagree on what they’ve told each other, study finds
Gus Cairns
Published: 22 September 2011
A US study on heterosexual couples at high risk of HIV finds that individuals’ interpretation of their relationship, their reporting of behaviour within the relationship and, especially, their recollection of whether they’ve disclosed sexual risks differ substantially between men and women.

Dr Kathy Hageman of the US Centers for Disease Control told the tenth AIDS Impact conference that, even in situations where the same proportion of men and women in the study agreed that a particular behaviour (such as condom use, anal sex or domestic violence) had happened, only about 50% of these behaviours were reported by both partners in the relationship.

This is one of the first studies attempting to quantify the degree of over- or under-reporting of sexual risks and other behaviours in couples,

The study was the Heterosexual Partner Study (HPS), a substudy of the high-risk heterosexual section of the National HIV Behavioral Surveillance System (NHBSS), a series of annual surveys that are conducted in the US annually in various high-prevalence areas. Surveys are carried out in different locations amongst men who have sex with men, injecting drug users and heterosexuals at high risk of HIV; another study from the NHBSS presented at AIDS Impact documented awareness of pre-exposure prophylaxis in gay men.

The study
The HPS had an innovative design. It recruited 855 women from the African-American and Hispanic communities. They had to be involved in at least one relationship with a man in the last year and to have had sex with that partner within the last three months. After completing the NHBSS and HPS questionnaires and being tested for HIV, they were asked to bring in at least one male partner to the research centre. The men then answered the same HPS questionnaire as the women.

The women brought in 926 male partners, with 71 women (7.6%) bringing in two partners [NB these figures are different from the ones reported in the conference abstract]. Eighteen per cent of the women were Hispanic and the rest black; 13% of male partners were Hispanic, 81% black and 11% of other ethnicity. The average length of couples’ relationships was three years. The average age of the women and the man was 33 and 35 respectively, but 37% of couples featured an age difference of five years or more (‘cross-generational’ sex is a known risk factor for HIV).

The male partners had many characteristics both of impoverished urban populations in the USA and of high HIV risk. No less than three-quarters of the men had been in jail at some time. Sixty-two per cent reported sexual partners outside the relationship, 31% crack use, 15% injecting drugs and 30% had been diagnosed with a sexually transmitted infection (STI). Two-thirds had ever taken an HIV test.

Women’s awareness of these factors varied a lot. If the man had been in jail, 77% of their female partners knew it; but only 43% knew whether their partner had taken an HIV test and only 27% if he had had an STI. In general, couples talked more freely about drugs than sex.

Disagreement on risk behaviours
The study compared women’s and men’s responses on a number of behaviours. It then looked at whether the male and female partners agreed whether a specific behaviour did or did not happen, or whether there was disagreement about whether it had happened.

Consistent condom use, for instance, was uncommon. Ten per cent of women and 9% of men reported using condoms consistently in vaginal sex. However even fewer, only 4%, of male/female pairs jointly agreed that they used condoms consistently. While 85% of couples agreed that they did not use them consistently, this left 12% of couples who did not agree on whether they used condoms consistently or not.

Similarly, 20% per cent of women and 25% of men said that they had had anal sex, but only 12% of couples jointly agreed they had. Two-thirds agreed that had not had anal sex, leaving 22% of couples in disagreement over whether they had or not (consistent condom use, by the way, was no more common in anal than vaginal sex).

The biggest disparity was over domestic violence – which was common. Twenty-eight per cent of both women and men agreed that it had occurred within the relationship. But only 13% of pairs jointly agreed that it had happened, while 57% agreed it had not. This meant that 29% of couples disagreed on whether (to use the questionnaire’s wording) the man had ever physically hurt the woman.
Disagreement on risk discussions
There was even less agreement on whether the couples had discussed specific STI and HIV risks. For instance, 22% of couples said yes, they had discussed whether the male partner had other lovers and 34% said no, they hadn’t discussed it, but 44% disagreed on whether the subject had been raised. Half the women and 45% of the men recalled discussing HIV status within the relationship, but only 27% of pairs agreed that they had discussed it, 36% agreed they hadn’t discussed in, and 43% couldn’t agree on whether they’d discussed it or not.

Men were consistently less likely to report that they had discussed a specific risk factor than women, but the gender difference varied according to the stigma attached to the subject. For instance approximately similar numbers of men and women recalled talking about HIV test results, which may be regarded as a responsible thing to do. But while 40% of women said they’d discussed whether their man had ever had sex with another man, only 16% of men said they had—and only 9% of couples agreed jointly that they had.

Dr Hageman commented on the wide disparity seen between individual and couple responses in the study, and said that efforts to address HIV prevention at the couple level had not been utilised as effectively as individual-level prevention efforts.

“Investigating couple agreement is an important step to understanding how partner-level dynamics impact HIV-related risk behavior and prevention efforts,” she said.

Reference

Crushing Kaletra tablets for kids leads to lower drug levels
Carole Leach-Lemens
Published: 23 September 2011
Using crushed lopinavir/ritonavir (Kaletra) tablets in children with HIV because of difficulties in swallowing whole tablets should be avoided, American researchers report in the advance online edition of the Journal of Acquired Immune Deficiency Syndromes.

Brookie M Best and colleagues undertook a randomised, open-label, cross-over study comparing whole and crushed tablets and the corresponding amounts of lopinavir/ritonavir detectable in the bloodstreams of HIV-infected children.

Drug levels were reduced by an average of 40% in children who received crushed tablets, but the reduction in drug levels varied from 5% to 75% between participants in the study. Using crushed Kaletra tablets could lead to potential drug failure as well as the risk of resistance in paediatric HIV patients, the researchers observed.

Lopinavir / ritonavir (Kaletra, also marketed as Aluvia in low and middle-income countries), a co-formulated protease inhibitor (PI), is recommended as first-line therapy for the treatment of HIV in infants, children and adolescents.

Lopinavir/ritonavir is also available in liquid form for infants and young children. It has an extremely unpleasant taste “with a high content (42%) of alcohol, creating the potential for significant alcohol toxicity with overdose, especially in infants”. It also has to be taken with food and requires refrigeration so making it a poor choice in resource-poor settings.

The availability of a paediatric smaller lopinavir/ritonavir tablet (100/25mg), note the authors, has improved acceptance among children. Nonetheless, they add, within their extensive HIV paediatric practice in the United States a considerable number of children and adolescents continue to have problems in swallowing the tablets or liquid form.

The lack of availability and a guaranteed continued supply of liquid and child- sized tablets in many settings means that adult pills are the primary means of antiretroviral treatment in children. The authors note that even in areas of established access, providers hesitate in using child tablets since supply is less reliable than for adult tablets.

Swallowing an adult-sized tablet can be difficult for children and may present choking risks in young children. Caretakers faced with these difficulties will consider giving the child broken or crushed tablets. The newer tablet form of Kaletra does not require refrigeration. Instructions clearly state that the tablet should not be crushed, broken or chewed based on studies in animals. These studies showed a 33% lower lopinavir and 61% lower ritonavir exposure in a crushed tablet compared to a whole one.

No evidence exists to support or dissuade providers from crushing tablets as a strategy for paediatric ART; no studies have been undertaken in humans on the effect of crushing tablets on drug exposure.
The authors undertook a prospective, randomised, open label, cross-over pharmacokinetic study in HIV-infected children taking Kaletra twice daily as part of their ART regimen. Eligibility included being between six and 17 years of age, having documented HIV infection and having taken Kaletra 200/50mg lopinavir/ritonavir tablets at standard paediatric doses for more than two weeks.

The children were randomised equally to study arms A and B. Arm A were given whole Kaletra tablets at the first visit and crushed tablets at the second visit. Children in Arm B got the drug in reverse order.

Study visits one and two consisted of the same procedures: Whole tablets were taken with six ounces of water. Tablets were crushed with a commercial pill crusher and mixed into four ounces of Jell-O brand pudding. Medicine remaining in the pill crusher was scraped out with a metal spatula and stirred into the pudding. Children had a standard breakfast (7 calories per kilo, 20% protein, 50% carbohydrates and 30% fat) and finished within 30 minutes of taking the drug. They ate freely throughout the day.

Blood was drawn before taking the drugs and then at 1, 2, 4, 6, 8 and 12 hours after taking the drug to measure the amount of lopinavir and ritonavir in the blood.

Twelve children aged 10-16 years of age enrolled between August 2008 and August 2009 were evaluated.

Exposure to both lopinavir and ritonavir is determined by a measure called area under the curve (AUC). Median lopinavir AUC after taking crushed and whole tablets was 92 mg*hr/l and 144 mg*hr/l, respectively with an AUC ratio of 0.55, \( p=0.003 \) and median ritonavir AUC of crushed and whole tablets was 7 mg*hr/l and 13.3 mg*hr/l respectively, with an AUC ratio of 0.53, \( p=0.006 \).

Lopinavir and ritonavir levels were thus decreased by 45% and 47%, respectively.

The authors conclude “Increased doses and therapeutic drug monitoring are needed to ensure adequate lopinavir/ritonavir exposure in patients requiring crushed Kaletra tablets. The reduced exposure with crushed Kaletra tablet dosing reinforces the need to discourage this dosing practice.”

Reference


Targeting HIV's sugar coating

New microbicide may block AIDS virus from infecting cells

SALT LAKE CITY, Sept. 23, 2011 – University of Utah researchers have discovered a new class of compounds that stick to the sugary coating of the AIDS virus and inhibit it from infecting cells – an early step toward a new treatment to prevent sexual transmission of the virus.

Development and laboratory testing of the potential new microbicide to prevent human immunodeficiency virus infection is outlined in a study set for online publication by Friday in the journal Molecular Pharmaceutics.

Despite years of research, there is only one effective microbicide to prevent sexual transmission of HIV, which causes AIDS, or acquired immune deficiency syndrome. Microbicide development has focused on gels and other treatments that would be applied vaginally by women, particularly in Africa and other developing regions.

To establish infection, HIV must first enter the cells of a host organism and then take control of the cells' replication machinery to make copies of itself. Those HIV copies in turn infect other cells. These two steps of the HIV life cycle, known as viral entry and viral replication, each provide a potential target for anti-AIDS medicines.

"Most of the anti-HIV drugs in clinical trials target the machinery involved in viral replication," says the study's senior author, Patrick F. Kiser, associate professor of bioengineering and adjunct associate professor of pharmaceutics and pharmaceutical chemistry at the University of Utah.

"There is a gap in the HIV treatment pipeline for cost-effective and mass-producible viral entry inhibitors that can inactivate the virus before it has a chance to interact with target cells," he says.

Kiser conducted the study with Alamelu Mahalingham, a University of Utah graduate student in pharmaceutics and pharmaceutical chemistry; Anthony Geonnotti of Duke University Medical Center in Durham, N.C.; and Jan Balzarini of Catholic University of Leuven in Belgium.

The research was funded by the National Institutes of Health, the Bill and Melinda Gates Foundation, the Catholic University of Leuven, Belgium, and the Fund for Scientific Research, also in Belgium.

Synthetic Lectins Inhibit HIV from Entering Cells

Lectins are a group of molecules found throughout nature that interact and bind with specific sugars. HIV is coated with sugars that help to hide it from the immune system. Previous research has shown that
lectins derived from plants and bacteria inhibit the entry of HIV into cells by binding to sugars found on the envelope coating the virus.

However, the cost of producing and purifying natural lectins is prohibitively high. So Kiser and his colleagues developed and evaluated the anti-HIV activity of synthetic lectins based on a compound called benzoboroxole, or BzB, which sticks to sugars found on the HIV envelope.

Kiser and his colleagues found that these BzB-based lectins were capable of binding to sugar residues on HIV, but the bond was too weak to be useful. To improve binding, they developed polymers of the synthetic lectins. The polymers are larger molecules made up of repeating subunits, which contained multiple BzB binding sites. The researchers discovered that increasing the number and density of BzB binding sites on the synthetic lectins made the substances better able to bind to the AIDS virus and thus have increased antiviral activity.

"The polymers we made are so active against HIV that dissolving about one sugar cube's weight of the benzoboroxole polymer in a bath tub of water would be enough to inhibit HIV infection in cells," says Kiser.

 Depending on the strain, HIV displays significant variations in its viral envelope, so it is important to evaluate the efficacy of any potential new treatment against many different HIV strains.

Kiser and his colleagues found that their synthetic lectins not only showed similar activity across a broad spectrum of HIV strains, but also were specific to HIV and didn't affect other viruses with envelopes.

The scientists also tested the anti-HIV activity of the synthetic lectins in the presence of fructose, a sugar present in semen, which could potentially compromise the activity of lectin-based drugs because it presents an alternative binding site. However, the researchers found that the antiviral activity of the synthetic lectins was fully preserved in the presence of fructose.

"The characteristics of an ideal anti-HIV microbicide include potency, broad-spectrum activity, selective inhibition, mass producibility and biocompatibility," says Kiser. "These benzoboroxole-based synthetic lectins seem to meet all of those criteria and present an affordable and scalable potential intervention for preventing sexual transmission in regions where HIV is pandemic."

Kiser says future research will focus on evaluating the ability of synthetic lectins to prevent HIV transmission in tissues taken from the human body, with later testing in primates. Kiser and his colleagues are also developing a gel form of the polymers, which could be used as a topical treatment for preventing sexual HIV transmission.

More Texas Schools Teach Safe Sex with Abstinence

*Morgan Smith*

Most Texas school districts that teach sex education choose abstinence-only programs, according to a forthcoming Texas Freedom Network analysis of Texas Education Agency data. However, a growing number of schools are moving toward abstinence-plus curricula that include instruction about contraceptive methods, condoms, and safer sex.

In the conservative west Texas town of Midland, 172 pregnant girls attended district public schools last year. "These are girls as young as 13 that are pregnant, some of them are on their second pregnancies," said Tracey Dees, the district’s health services supervisor, noting many students also report STDs. Eighteen months ago, the board chose to implement a new comprehensive curriculum for seventh and eighth grades.

In Harris County, nine districts have or are adopting an abstinence-plus program, said Susan Tortolero, director of University of Texas’ Prevention Research Center, who developed the Midland curriculum. “It’s like we’re beyond this argument of abstinence, abstinence-plus,” she said. “Districts want something that works.”

Districts in Austin, Corpus Christi, San Antonio, and Plano also have moved toward comprehensive sex education. Research shows that teaching teens about condoms and birth control delays, rather than encourages, sexual initiation, Tortolero said.

The Spring Branch Independent School District outside Houston began examining abstinence-plus programs about three years ago. After seeing a slight increase in pregnancies and reviewing behavioral trends, the district will implement the new curriculum next year, said Rebecca Fuchs, the district’s director of health and fitness.

Texas had the third-highest rate of births among teens ages 15-19 in the nation, according to 2008 data from the National Center for Health Statistics. Last year, the state health department decided not to
apply for federal comprehensive sex education funding. Texas remains the largest recipient of federal abstinence-only grants.

**Circumcision Among Men Who Have Sex with Men in London, United Kingdom: An Unlikely Strategy for HIV Prevention**

*Sexually Transmitted Diseases Vol. 38; No. 10: P. 928-931, (10..2011) Alicia C. Thornton; Samuel Lattimore; Valerie Delpech; Helen A. Weiss; Jonathan Ellford*

Male circumcision is unlikely to be a workable HIV prevention strategy among London MSM, the current study suggests. The team undertook the research to explore attitudes about circumcision among MSM in London and to assess the feasibility of conducting research on circumcision and HIV prevention among these men.

In May and June 2008, a convenience sample of MSM visiting gyms in central London completed a confidential, self-administered questionnaire. The information collected included demographic characteristics, self-reported HIV status, sexual behavior, circumcision status, attitudes about circumcision, and willingness to take part in research on circumcision and HIV prevention.

Among the 653 participants, 29 percent reported they were circumcised. HIV prevalence among the MSM was 23.3 percent and did not differ significantly between circumcised (18.6 percent) and uncircumcised (25.2 percent) men (adjusted odds ratio=0.79; 95 percent confidence interval: 0.50-1.26). The proportion of participants reporting unprotected anal intercourse in the past three months was similar in the circumcised (38.8 percent) and uncircumcised (36.7 percent) groups (AOR=1.06; 95 percent CI: 0.72-1.55). The uncircumcised MSM were less likely to think there were benefits to being circumcised compared to the circumcised men (31.2 percent vs. 65.4 percent, P<0.001). Just 10.3 percent of the uncircumcised men indicated a willingness to take part in research on circumcision as a strategy to prevent HIV transmission.

“Most uncircumcised MSM in this London survey were unwilling to participate in research on circumcision and HIV prevention,” the authors concluded. “Only a minority of uncircumcised men thought that there were benefits of circumcision. It is unlikely that circumcision would be a feasible strategy for HIV prevention among MSM in London.”

**Vaccination Must Be Part Of Response To Cholera Outbreak In Haiti**

Though "[c]holera vaccines are not a magic bullet and are not available in adequate numbers" to vaccinate everyone in Haiti, where at least 10 people die each day in an outbreak that began in October 2010, "there are compelling reasons to add vaccinations to the arsenal of public health weapons that has been deployed against cholera in Haiti," a Washington Post editorial states. Efforts to improve access to clean water, educate the public about cholera transmission and treat those infected are ongoing, "[b]ut those efforts should be supplemented with an ambitious vaccination program starting as soon as practicable," the editorial writes.

The cost of vaccinating every person in Haiti would cost about $20 million, according to the editorial, which notes a "recent study showed that if only five percent of the population in the most vulnerable areas were vaccinated, it would cut the number of cholera cases by 11 percent, and if 30 percent of Haitians got the vaccine, it would reduce infections by 55 percent and save 3,320 lives." The editorial concludes, "Surely that would be a worthwhile return on a very modest investment" (9/22).

**New targets for the control of HIV predicted using a novel computational analysis**

A new computational approach has predicted numerous human proteins that the human immunodeficiency virus (HIV) requires to replicate itself. These discoveries "constitute a powerful resource for experimentalists who desire to discover new targets for human proteins that can control the spread of HIV," according to the authors of this study that appears in the Sept. 22, 2011 issue of *PLoS Computational Biology*, a journal published by the Public Library of Science.

The authors of the article are: T. M. Murali, a computer scientist, and Brett Tyler of the Virginia Bioinformatics Institute http://www.vbi.vt.edu/faculty/personal/Brett_Tyler, both located at Virginia Tech, and Michael G. Katze, a microbiologist and associate director of the Washington National Primate Research Center at the University of Washington.

David Badger of Blacksburg, Va., one of Murali's graduate students, and Matthew D. Dyer of Applied Biosystems of Foster City, Cal., also contributed to the study, which was funded by grants from the
When a person contracts HIV, it causes the progressive failure of the body's immune system, with the onset of life threatening infections and diseases such as cancer. Over 25 years of intensive research have failed to create a vaccine for preventing HIV. Moreover, drugs used to cure HIV become rapidly ineffective because HIV is able to develop mutations against drugs, Murali said.

A recent line of research is examining whether human proteins can be targeted to cure HIV. Since viruses such as HIV have very small genomes, they must exploit the cellular machinery of the host to spread. Therefore, disrupting the activity of selected host proteins may impede viruses. Moreover, since human proteins evolve at a much slower rate than HIV proteins, human proteins that are targeted by drugs are very unlikely to develop mutations that render the drugs ineffective.

In fact, three studies published in 2008 systematically silenced virtually every human gene in order to discover HIV Dependency Factors (HDFs), i.e., those genes that are necessary for HIV to survive and replicate. Each of these three studies discovered hundreds of HDFs. However, a puzzling aspect was that only a handful of HDFs were common to two or more experiments.

"We set out to untangle this mystery," Murali said. "We hypothesized that many HDFs have not yet been discovered. Other papers had suggested that HDFs may themselves interact with each other. Inspired by these observations, we hypothesized that we could predict new HDFs by exploiting the proximity between HDFs within networks of interactions between human proteins."

To this end, they used an algorithm called SinkSource developed by Murali and Tyler. Tyler explained the algorithm using this analogy: "We treated the human protein network as if it were a system of tanks connected by pipes carrying water. This arrangement allowed us to study the flow of predictive information (water) from proteins we are certain about (full tanks) to those we are uncertain about (empty tanks). The further you get from the full tanks, the weaker the trickle, and the less water accumulates in the bottom of the tank. Mathematically you can show that, over time, every empty tank accumulates some stable level of water. At the end of the analysis, tanks accumulating lots of water were judged to be good predictions."

"We found that SinkSource and one of its variants made predictions of very high quality," Murali added. "We evaluated predicted HDFs using a number of additional datasets that we did not use during the prediction step."

Their most exciting results used an analysis of HDF activities in two non-human primate species that respond differently to Simian Immunodeficiency Virus (SIV). One species, the African green monkey, does not develop disease when infected by SIV, in contrast to the other species, pig-tailed macaque. Using data already published by Katze, the authors showed that predicted HDFs had very different patterns of expression in the two species, especially in lymph nodes and within 10 days after infection with the virus. They also showed that predicted HDFs participated in human cellular processes that are known to be subverted by the virus, including gene transcription and translation, energy production, protein degradation, and transport across the nuclear membrane. Moreover, many predicted HDFs themselves directly interacted with proteins in HIV.

From these results, Murali, Tyler, and Katze concluded that existing genomic screens are "incomplete and many HDFs are yet to be discovered experimentally. Our results suggest that many HDFs are yet to be discovered and that they have potential value as prognostic markers to determine pathological outcome and the likelihood of Acquired Immune Deficiency Syndrome (AIDS) development."

Close Up Look at a Microbial Vaccination Program:

**Berkeley Lab Researchers Resolve Sub-nanometer Structure of Cascade, an Ally for Human Immune System**

September 22, 2011

Lynn Yarris (510) 486-5375 leyarris@lbl.gov

This movie shows the conformation of Cascade’s subunits – CasA (purple), CasB (yellow) and CasE (magenta) – being rearranged while the helical spine of the complex remains relatively undisturbed.

A complex of proteins in the bacterium *E.coli* that plays a critical role in defending the microbe from viruses and other invaders has been discovered to have the shape of a seahorse by researchers with the U.S Department of Energy’s Lawrence Berkeley National Laboratory (Berkeley Lab). This discovery holds far more implications for your own health than you might think.
In its never-ending battle to protect you from infections by bacteria, viruses, toxins and other invasive elements, your immune system has an important ally – many allies in fact. By the time you reach adulthood, some 90-percent of the cells in your body are microbial. These microbes – collectively known as the microbiome – play a critical role in preserving the health of their human host.

“Perturbations of the human microbiome by viral and other infections can disrupt important symbioses and open the door to invasions by human pathogens,” says Blake Wiedenheft, a biochemist with Berkeley Lab and the University of California (UC) Berkeley. “By understanding the mechanisms behind microbial immune systems, we can better understand how they are similar and where they are different from the human immune system.”

Wiedenheft is part of a team of researchers, led by biochemist Jennifer Doudna, a leading authority on RNA molecular structures, and biophysicist Eva Nogales, an expert on electron microscopy and image analysis, that has provided the first sub-nanometer look at a central player in the microbial immune system. Through a combination of cryo-electron microscopy and three-dimensional image reconstruction, they have determined the structure of a protein complex called “Cascade,” that acts as a surveillance system for detecting and inactivating the nucleic acid of invading pathogens.

From left, Blake Wiedenheft, Eva Nogales, Gabriel Lander and Jennifer Doudna, used a combination of cryo-electron microscopy and 3-D image reconstruction to determine the structure of Cascade, a protein complex that detects and inactivates invading pathogens. (Photo by Roy Kaltschmidt, Berkeley Lab)

Doudna and Nogales are the corresponding authors and Wiedenheft and Gabriel Lander are the lead authors of a paper describing this research in the journal Nature. The paper is titled “Structures of the RNA-guided surveillance complex from a bacterial immune system.” Like Wiedenheft, Doudna, Nogales and Lander all hold joint appointments with Berkeley Lab and UC Berkeley. Doudna and Nogales are also investigators with the Howard Hughes Medical Institute (HHMI). Wiedenheft is an HHMI fellow, and Lander a fellow with the Damon Runyon Cancer Research Foundation.

The microbial immune system can be likened to a vaccination program because of the adaptive-type nucleic acid-based line of defense deployed by a unit of DNA called CRISPR, which stands for Clustered Regularly Interspaced Short Palindromic Repeats. Although CRISPR defense systems are only found in microbes, they are analogous to the way in which the human immune system deploys short interfering RNAs (siRNAs) to fight off infections or correct genetic problems.

Usually located on a microbe’s chromosome, CRISPR units consist of “repeats,” base-pair sequences ranging from 30 to 60 nucleotides in length, that are separated by “spacers,” variable sequences, which are also 30 to 60 nucleotides in length. A microbe might harbor several CRISPR loci (sites) within its genome and each locus might contain between four and 100 CRISPR repeat-spacer units. When a microbe recognizes that it has been invaded, it incorporates a small piece of the invader’s DNA into one of its CRISPR units as a new spacer sequence.

“By integrating short fragments of foreign DNA into its CRISPR units, a microbe maintains a genetic record of all prior encounters with foreign transgressors,” says Doudna. “CRISPRs are transcribed and the long primary transcript is processed into a library of short CRISPR-derived RNAs (crRNAs), each of which contains a unique sequence that is complementary to a foreign nucleic acid challenger.”

In Escherichia coli, crRNAs are incorporated into the Cascade complex – Cascade stands for CRISPR-associated complex for antiviral defense. It is the mission of Cascade to detect and engage foreign DNA. Cascade will release crRNAs that will bind with foreign nucleic acid sequences – via base pair matching to a “seed” sequence of nucleotides – and silence or otherwise inactivate them. Cascade will also send out signals to recruit the enzyme Cas3 to join the battle. Cas3 is a single-stranded nuclease that can cleave foreign DNA into harmless pieces.

To learn how Cascade is able to carry out its mission, Doudna, Nogales, Wiedenheft, Lander and a team of colleagues determined the sub-nanometer structures of Cascade before and after binding to a target sequence of foreign DNA. They discovered Cascade’s seahorse-shaped architecture and found that crRNAs are displayed along the spine of the seahorse within a helical arrangement of protein subunits.
The architecture of the Cascade protein complex, a key player in the microbial immune system, resembles a seahorse, with crRNAs (green) displayed along the backbone within a helical arrangement of Cas protein subunits.

“The rigid backbone of this seahorse shaped architecture helps explain how the Cascade complex is able to accommodate crRNAs in a way that simultaneously protects them from degradation while maintaining their availability for base pairing to an invading nucleic acid target,” Wiedenheft says. “We further speculate that Cascade may pre-order a portion of the crRNA in a helical configuration and that this mechanism may be a structural solution for RNA-guided target binding that has been conserved through evolution.”

Although its seahorse shape is maintained throughout Cascade’s engagement with the enemy, the binding of the crRNAs to a foreign target does induce a “concerted conformational change” in the helical protein subunits running along Cascade’s backbone.

Says Nogales, “We speculate that this conformational change in the protein subunits generates a signal for recruiting Cas3 for further degradation of invading nucleic acid sequences.”

Cascade is a small complex by electron microscopy standards and its asymmetric conformation presented a major challenge that required the acquisition of a large amount of data during what Lander describes as “marathon” collection sessions.

“Three dimensional processing of electron microscopy data is generally a slow and iterative process, starting with very low resolution blobs that over time take shape and provide more intricate details,” says Lander. “Given Cascade’s seahorse shape, it was a bit like watching an embryo grow into a fully developed Cascade with a corkscrew spine. This is the very special kind of specimen that microscopists dream of.”

In addition to Doudna, Nogales, Wiedenheft and Lander, other co-authors of the Nature paper “Structures of the RNA-guided surveillance complex from a bacterial immune system” were Kaihong Zhou, Matthijs Jore, Stan Brouns and John van der Oost.

New treatment for kala azar, the most deadly parasitic disease after malaria
Urgent support needed for governments to roll out treatments and control disease
[23 September 2011, Nairobi, Kenya]

East Africa is fighting the worst kala azar outbreak in a decade. Collaboration across the region through the Leishmaniasis East Africa Platform (LEAP) has resulted in the development of a new combination therapy (SSG&PM) which is cheaper and nearly halves the length of treatment from a 30 day course of injections to 17 days. East African endemic countries are taking the necessary regulatory measures to use it in their programmes, but experts warn that without international funding or interest in supporting governments in the roll out, too few patients will benefit.

“The poorest of the poor, in the most remote villages are the ones who are wasting away from kala azar and who could benefit the most from a shorter more affordable treatment” said Dr. Monique Wasunna, Assistant Director, KEMRI, and Head, DNDi Africa. “Neglected diseases and patients mean that even when there are new treatments and hope, they are too far from the headlines and donor priorities to get support to governments. This is why we are calling for urgent action.”

This week in Nairobi, over 100 clinical researchers and regional experts from Ministries of Health and drug regulatory authorities are meeting for the bi-annual LEAP – Leishmaniasis East Africa Platform – to see what is and is not working in the field and to find better ways to control the disease.

After 70 years of little improvement or change in the treatment of kala azar in Africa, LEAP and its partners have developed a new treatment: Sodium Stibogluconate & Paromomycin (SSG&PM) combination treatment. This is cheaper and nearly halves the length of treatment from the current 30 day course of injections to 17 days. It also cures the patient. Combination therapies help fight resistance to treatment. Countries around the region are in the process of registration and are ready to use the treatment, but need funding to control the disease.

Kala azar is another name given to visceral leishmaniasis (VL), a parasitic disease endemic in around 70 countries worldwide. South Sudan has the second highest number of cases after India. The disease is spread through the bite of a sandfly and is fatal without treatment. Approximately half a million people
are infected with the disease and 50-60,000 die every year as a result of the infection. Patients suffer from irregular bouts of fever, substantial weight loss, swelling of the spleen and liver, and anaemia.

“I have spent fifty years treating kala azar patients and researching this killer parasite and I know first-hand how desperately these poor patients and overburdened health workers need shorter, cheaper, and easier-to-use treatment,” said Professor Ahmed Mohamed El Hassan, Emeritus Professor, Institute of Endemic Diseases University of Khartoum, Sudan. “Ideally for patients in such conditions, we need an oral treatment, such as those being tested or completely new drugs, but we are a long way from there and we need to make the most of this existing better treatment and find the funds to roll it out,” he concluded.

In March 2010, the World Health Organization (WHO) Expert Committee on the Control of Leishmaniases recommended SSG&PM as first-line treatment for VL in East Africa. It is already being used to treat patients in the countries such as Sudan and South Sudan. Other affected countries are in the process of registering PM to combine it with the already registered SSO to get the treatment to patients.

“After 20 years, WHO has updated the guidelines for the control of leishmaniasis. This shows that there is greater collaboration and progress. Now countries need support to translate this into lives saved on the ground,” said Dr. Mercé Herrero, Disease Prevention and Control, Leishmaniasis National Control Programme, WHO Ethiopia.

**Virus Discovery Helps Scientists Predict Emerging Diseases**

ScienceDaily (Sep. 22, 2011) — Fresh insight into how viruses such as SARS and flu can jump from one species to another may help scientists predict the emergence of diseases in future. Researchers have shown that viruses are better able to infect species that are closely related to their typical target species than species that are distantly related.

Their results suggest that when diseases make the leap to a distant species—such as bird flu infecting humans—they may then spread easily in species closely related to the new victim, regardless of how closely related these are to the original target species.

Scientists from the Universities of Edinburgh and Cambridge looked at how relationships between species might determine the spread of an important group of emerging diseases, known as RNA viruses. This group of diseases includes HIV, SARS and flu.

By infecting more than 50 species of flies with three different viruses, the researchers showed that species closely related to a virus’s usual target species were more susceptible than distantly related flies. They also showed that groups of flies that were closely related were similarly susceptible to the same viruses.

The study, funded by the Biotechnology and Biological Sciences Research Council, Natural Environment Research Council, the Wellcome Trust and the Royal Society, was published in the journal *PLoS Pathogens*.

Dr Ben Longdon of the University of Edinburgh’s School of Biological Sciences, who led the study, said: “Emerging diseases such as SARS, HIV and some types of flu have all got into humans from other species. Understanding how diseases jump between different species is essential if we want to predict the appearance of new diseases in the future.”

**Journal Reference:**


**Rates of gonorrhoea, chlamydia surge**

**Belinda Tasker, AAP Medical Correspondent**

*September 27, 2011—12:04AM*

Australia is in the grip of a gonorrhoea and chlamydia epidemic following a surge in cases in the past year.

Newly diagnosed cases of chlamydia leapt 17 per cent to 74,305 in 2010, while those for gonorrhoea rose 25 per cent to just exceed 10,000.

The figures featured in the latest surveillance report on HIV, viral hepatitis and sexually transmitted infections (STIs) released on Tuesday by the University of NSW’s Kirby Institute.

The institute’s Associate Professor David Wilson said the rise in gonorrhoea and chlamydia cases was partly due to more people being tested in response to public education campaigns.

"However, what we are seeing right now is the rate of diagnosis is surpassing the rate of testing, so that indicates there's an increase in overall infection levels," he said.

"So there's an epidemic.
"Almost 75,000 people were diagnosed with chlamydia last year. That's phenomenal. That's more than any other country."

Chlamydia and gonorrhoea can affect women and men who have sex with an infected partner. Both STIs are treatable with antibiotics, but they can be hard to diagnose because infected people often show no symptoms.

If left untreated in women, the infections can lead to pelvic inflammatory disease (PID), which is the main cause of infertility.

Assoc Prof Wilson attributed the rise in the number of chlamydia and gonorrhoea cases to men failing to practice safe sex by using condoms.

Young heterosexual people were the most likely to be infected with chlamydia, the most common STI in Australia, while men who have sex with men were the most likely to have gonorrhoea.

Young people aged 15 to 29 accounted for 80 per cent of the total cases of chlamydia diagnosed during the year.

The increase in cases among women was almost quadruple the rise seen in 2009, while men showed a more than threefold increase.

There were substantially higher rates for both STIs among Aborigines and Torres Strait Islanders.

Indigenous people accounted for more than a third of all gonorrhoea cases and nine per cent of chlamydia cases.

Meanwhile, HIV and viral hepatitis remained at fairly stable levels in 2010.

The number of new HIV diagnoses was 1043, pushing the total number of cases recorded in Australia above 30,000 for the first time.

Australian Federation of AIDS Organisations executive director Rob Lake said while Australia had done well to contain the number of new HIV cases to about 1000 a year, it was time to "move beyond this plateau and decrease infection rates".

He said Australia had committed to a United Nations goal of halving new HIV infection rates before 2015 and one of the best ways of achieving that would be by introducing rapid HIV testing.

"Overseas experience has shown that when rapid (an initial result within an hour) HIV testing is offered, testing rates increase, and many people who have never previously tested present for testing," Mr Lake said.

**Brown to Decide State's HPV Vaccine Debate**

_Sacramento Bee_ (09.24.2011) Torey Van Oot

A measure awaiting action by Gov. Jerry Brown would allow youths age 12 and older to receive STD prevention services without parental consent.

AB 499 is sponsored by Assembly member Toni Atkins (D-San Diego). While it does not make prevention services mandatory, the bill aims to boost minors’ access to services including vaccination against human papillomavirus (HPV) and hepatitis, and HIV post-exposure prophylaxis.

“What this adds is them being able to receive prevention ... which is obviously a very important part of health care,” said Dr. Dorothy Furgerson, chief medical officer for Planned Parenthood Mar Monte. “If you can prevent a cancer with a vaccine, shouldn’t you do that?”

AB 499 sets 12 as the minimum age for receiving preventive services without parental consent, aligning it with existing law on treatment and conforming to federal age guidelines for HPV vaccination.

Some parents are not involved in making health care decisions for their children, supporters say, and increasing access to preventive services could help combat rising STD rates in young people.

But a coalition of vaccine opponents, family groups, and others says the bill takes away parents’ rights. Brown’s office has received so many calls about AB 499 that it has set up a voicemail box exclusively for the issue. The governor has not taken a position on the measure.

Anti-vaccine activist Dawn Winkler, executive director of Health Advocacy in the Public Interest, worries youths may feel pressured to get vaccinated without fully understanding the potential side effects.

“It’s just a matter of how can a 12-year-old possibly assess risk-vs.-benefit information and make a medical decision for themselves without the knowledge or consent of their parent?” she asked.

**Surgeons Object to New CDC Organ-Screening Guidelines**

_Wall Street Journal_ (09.22.2011) Laura Landro

New draft guidelines for reducing the risk of HIV and hepatitis B and C virus (HBV, HCV) transmission through solid organ transplants are too restrictive, according to the head of the American Society of
Transplant Surgeons. The CDC proposal issued Wednesday is open to public comment for 60 days, and ASTS plans to weigh in during the process, said Mitchell Henry, its president.

“We support guidelines which help to decrease disease transmission, but we want them to be evidence-based and balanced by the risks of dying without an organ transplant,” Henry said.

Using the more sensitive and expensive nucleic acid test — for HIV, HCV, and under certain circumstances HBV — would not always be feasible, such as when an organ is flown to a remote location where no labs are available, Henry added.

ASTS believes the expansion of donors considered risky includes too many population groups that might otherwise be good candidates, Henry said. Potential donors who have had sex with two or more partners in the last year “could cover three-quarters of college kids in America,” he noted.

While the guidelines are not enforceable, they often become mandatory standards of care, Henry said. ASTS plans to submit criticism that its concerns have not been taken into account, as well as suggestions about how to modify the guidelines.

The draft rules are meant to give potential organ recipients and their physicians as much information as possible about transmission risks so they can make informed decisions, said Dr. Matthew J. Kuehnert, director of CDC's Office of Blood, Organ, and Other Tissue Safety.

“The guidelines may actually expand available organs by providing more confidence in the risk assessment of the donor, which will in turn improve the chances a patient and doctor will accept the organ,” said Kuehnert.

For more information about the proposal, visit: http://www.regulations.gov/#!docketDetail;dct=FR%252BPR%252BN%252BO%252BSR;rpp=10;po=0;D=CDC-2011-0011.

More Youngsters Having Unsafe Sex: Global Study

 Reuters , (09.25.2011)

Since 2009, the numbers of youths reporting sex with a new partner without using contraception grew from 19 percent to 40 percent in France, from 38 percent to 53 percent in the United States, and from 36 percent to 43 percent in Great Britain, a new survey suggests. Undertaken on behalf of hormonal contraceptive maker Bayer HealthCare Pharmaceuticals, the survey of more than 6,000 people in 29 countries was released ahead of World Contraception Day, Sept. 26, and endorsed by 11 non-governmental reproductive health organizations.

Among the report’s findings:

• *Just 55 percent of young people in Europe reported receiving school-based sex education, compared to 78 percent in Latin America, 76 percent in Asia Pacific, and 74 percent in the United States.*

• *Being too embarrassed to speak honestly with a health care professional was a major barrier to contraception, cited by 42 percent of youths lacking access in Asia Pacific, 38 percent in Europe, 27 percent in Latin America and 24 percent in United States.*

• *Bathing or showering after sex was cited as possibly contraceptive by more than a third of Egyptian respondents.*

• *More than a quarter of participants in Thailand and India believed sex during menstruation was effectively contraceptive.*


Scientists Find H1N1 Flu Virus Prevalent in Animals in Africa ***

ScienceDaily (Sep. 26, 2011) — UCLA life scientists and their colleagues have discovered the first evidence of the H1N1 virus in animals in Africa. In one village in northern Cameroon, a staggering 89 percent of the pigs studied had been exposed to the H1N1 virus, commonly known as the swine flu.

"I was amazed that virtually every pig in this village was exposed," said Thomas B. Smith, director of UCLA's Center for Tropical Research and the senior author of the research. "Africa is ground zero for a new pandemic. Many people are in poor health there, and disease can spread very rapidly without authorities knowing about it."

H1N1 triggered a human pandemic in the spring of 2009, infecting people in more than 200 countries. In the U.S., it led to an estimated 60 million illnesses, 270,000 hospitalizations and 12,500 deaths, according to the Centers for Disease Control. The virus, known scientifically as Influenza A (H1N1), is made up of genetic elements of swine, avian and human influenza viruses. The pigs in Cameroon, the researchers say, were infected by humans.
"The pigs were running wild in that area," said lead author Kevin Njabo, a researcher in UCLA’s department of ecology and evolutionary biology and associate director of the Center for Tropical Research. "I was shocked when we found out it was H1N1. Any virus in any part of the world can reach another continent within days by air travel. We need to understand where viruses originate and how they spread, so we can destroy a deadly virus before it spreads. We have to be prepared for a pandemic, but so many countries are not well-prepared—not even the United States."

Njabo and his colleagues randomly collected nasal swabs and blood samples from domestic pigs that were part of 11 herds in villages and farms in Cameroon in 2009 and 2010. The results are published in the current issue of Veterinary Microbiology, a peer-reviewed scientific journal specializing in microbial animal diseases.

Nasal swabs can detect a current infection, and blood samples reveal past exposure to a virus. Because an active infection lasts only about five days, "we have to be lucky to get an active infection in the field, but evidence of the infection stays in the blood."

In the village in northern Cameroon, Njabo found two pigs with active H1N1 infections, and virtually every other pig had evidence of a past infection in its blood.

"The pigs got H1N1 from humans," Njabo said. "The fact that pigs in Africa are infected with the H1N1 flu virus illustrates the remarkable interconnectedness of the modern world with respect to diseases. The H1N1 virus that we found in livestock in Cameroon is virtually identical to a virus found in people in San Diego just a year earlier, providing an astonishing example of how quickly the flu can spread all over the globe."

"The discovery of H1N1 in African swine is also important because it shows how farming practices can trigger disease outbreaks and suggests opportunities for improving human and livestock health. Our studies indicate that H1N1 infections are more common in swine that wander freely in villages than in animals that are confined to farms."

The biologists used a diagnostic test called ELISA—enzyme-linked immunosorbent assay—to test for potential viruses. ELISA revealed the pigs had the human strain of H1N1.

Viruses in pigs can mix into a much more virulent strain that can spread extremely fast, Smith and Njabo warned.

"We are studying the interface between viruses in humans, wild animals and domestic animals and how viruses move among them," Njabo said.

**A pandemic as in 'Contagion' could occur**

"This particular H1N1 strain is ubiquitous," said Smith, who is also a professor of ecology and evolutionary biology and a member of UCLA’s Institute of the Environment and Sustainability. "When different strains of influenza are mixed in pigs, such as an avian strain with a human strain, you can get new hybrid strains that may affect humans much more severely and can potentially produce a pandemic that can allow human-to-human infection. This is how a pandemic can arise; we need to be very vigilant.

"It would be comforting to believe that the deaths of tens of millions of people, or more, as depicted in the movie 'Contagion' is merely science fiction, but something that resembles what is depicted there could happen under a certain set of circumstances."

In the 20th century, the world experienced three influenza pandemics that collectively killed more than 40 million people, Smith and Njabo noted.

In addition to studying pigs, Njabo and colleagues have also collected samples from hundreds of wild birds, ducks and chickens in Cameroon and Egypt. Their colleagues at other institutions are conducting similar studies in China, Bangladesh and elsewhere.

Smith and Njabo work with UCLA’s Global Bio Lab, in collaboration with Hilary Godwin, a professor of environmental health sciences at the UCLA School of Public Health, to identify new diseases, speed up the development of new vaccines and try to prevent the next pandemic.

"The world is a global village; no area is truly isolated," said Njabo, who was born and raised in Cameroon. "There are so many unknowns about the transmission rates of viruses between humans and wild animals. We have to expand screening."

Since 2007, Njabo has gone to Cameroon two to three times a year to collect samples and is there currently. He informed the government’s Ministry of Livestock, Fisheries, and Animal Industries of the findings to try to reduce the spread of the disease. Smith, Njabo and colleagues will hold a workshop in Cameroon next year to tell people how to raise pigs in a way that reduces the risk of disease.
New Targets for the Control of HIV Predicted Using a Novel Computational Analysis

ScienceDaily (Sep. 23, 2011) — A new computational approach has predicted numerous human proteins that the human immunodeficiency virus (HIV) requires to replicate itself. These discoveries "constitute a powerful resource for experimentalists who desire to discover new targets for human proteins that can control the spread of HIV," according to the authors of this study that appears in the Sept. 22, 2011 issue of PLoS Computational Biology, a journal published by the Public Library of Science.

When a person contracts HIV, it causes the progressive failure of the body's immune system, with the onset of life threatening infections and diseases such as cancer. Over 25 years of intensive research have failed to create a vaccine for preventing HIV. Moreover, drugs used to cure HIV become rapidly ineffective because HIV is able to develop mutations against drugs, Murali said.

A recent line of research is examining whether human proteins can be targeted to cure HIV. Since viruses such as HIV have very small genomes, they must exploit the cellular machinery of the host to spread. Therefore, disrupting the activity of selected host proteins may impede viruses. Moreover, since human proteins evolve at a much slower rate than HIV proteins, human proteins that are targeted by drugs are very unlikely to develop mutations that render the drugs ineffective.

In fact, three studies published in 2008 systematically silenced virtually every human gene in order to discover HIV Dependency Factors (HDFs), i.e., those genes that are necessary for HIV to survive and replicate. Each of these three studies discovered hundreds of HDFs. However, a puzzling aspect was that only a handful of HDFs were common to two or more experiments.

"We set out to untangle this mystery," Murali said. "We hypothesized that many HDFs have not yet been discovered. Other papers had suggested that HDFs may themselves interact with each other. Inspired by these observations, we hypothesized that we could predict new HDFs by exploiting the proximity between HDFs within networks of interactions between human proteins."

To this end, they used an algorithm called SinkSource developed by Murali and Tyler. Tyler explained the algorithm using this analogy: "We treated the human protein network as if it were a system of tanks connected by pipes carrying water. This arrangement allowed us to study the flow of predictive information (water) from proteins we are certain about (full tanks) to those we are uncertain about (empty tanks). The further you get from the full tanks, the weaker the trickle, and the less water accumulates in the bottom of the tank. Mathematically you can show that, over time, every empty tank accumulates some stable level of water. At the end of the analysis, tanks accumulating lots of water were judged to be good predictions."

"We found that SinkSource and one of its variants made predictions of very high quality," Murali added. "We evaluated predicted HDFs using a number of additional datasets that we did not use during the prediction step."

Their most exciting results used an analysis of HDF activities in two non-human primate species that respond differently to Simian Immunodeficiency Virus (SIV). One species, the African green monkey, does not develop disease when infected by SIV, in contrast to the other species, pig-tailed macaque. Using data already published by Katze, the authors showed that predicted HDFs had very different patterns of expression in the two species, especially in lymph nodes and within 10 days after infection with the virus. They also showed that predicted HDFs participated in human cellular processes that are known to be subverted by the virus, including gene transcription and translation, energy production, protein degradation, and transport across the nuclear membrane. Moreover, many predicted HDFs themselves directly interacted with proteins in HIV.

From these results, Murali, Tyler, and Katze concluded that existing genomic screens are "incomplete and many HDFs are yet to be discovered experimentally. Our results suggest that many HDFs are yet to be discovered and that they have potential value as prognostic markers to determine pathological outcome and the likelihood of Acquired Immune Deficiency Syndrome (AIDS) development."

Journal Reference:
Haiti: Early HIV treatment cost-effective in one of the world’s poorest countries
Carole Leach-Lemens
Published: 28 September 2011
Starting HIV treatment early, when CD4 cell counts fell below 350 cells/mm$^3$ in accordance with current World Health Organization (WHO) recommendations, was cost-effective compared to starting at 200 cells/mm$^3$ (standard ART) over a three-year period in Haiti, American and Haitian researchers report in the September 11 edition of *PloS Medicine*.

Haiti is one of the world’s poorest countries, lying in the bottom 10% of countries by GDP per capita in 2010. It is the poorest nation in the western hemisphere.

Serena P Koenig and colleagues did a cost-effectiveness study of early compared to standard ART using data from a prospective randomised trial (CIPRA HT-001). The trial was undertaken in 2009 at the Center of the Haitian Group for the Study of Kaposi’s Sarcoma and Opportunistic Infections (GHESKIO) among HIV-infected patients with a CD4 cell count between 200 and 350 cells/mm$^3$.

The trial showed early ART compared to standard ART reduced death rates by 75% after a median follow-up of 21 months.

After three years the total cost of saving one life by starting ART early rather than waiting until the CD4 cell count was under 200 cells/mm$^3$ was US$2,050 with research-related costs excluded (95% CI: US$722/YLS-US$5,537/YLS).

WHO’s formula for the cost-effectiveness of a medical intervention is defined as less than three times a country’s gross domestic product (GDP) for each person for each disability-adjusted life year saved (DALY) and very cost-effective if under one times the GDP.

The authors used years of life saved (YLS) rather than DALY and note YLS is generally acceptable in this formula. The threshold in Haiti in 2009 was US$2,355/YLS. The GDP for each person in Haiti is US$785.

In November 2009 based on the results of the CIPRA HT-001 trial together with a post hoc analysis within the SMART trial WHO changed its guidelines for starting ART to when CD4 cell counts fell below 350 cells/mm$^3$ rather than 200 cells/mm$^3$. The panel responsible for the recommendations “placed a high value on avoiding death, disease progression and HIV transmission over and above cost and feasibility.”

At the end of 2009 in low- and middle-income countries an estimated 14.5 million were in need of ART yet only 5.3 million were getting it; and in Haiti, with an estimated prevalence of 2.2%, an estimated 43% (26,000) of people with CD4 cell counts below 350 cells/mm$^3$ were on ART.

Policy makers in low- and middle-income countries have to make difficult decisions in how to allocate and make the best use of limited resources.

Putting the guidelines into practice will be determined in large part by knowing whether it is cost-effective.

The authors, in what they believe to be the first analysis of its kind, compared the costs and survival benefits of early to standard ART using data from a randomised clinical trial (CIPRA HT-001) that compared these two strategies in HIV-infected adults with no history of an AIDS-defining illness and a CD4 cell count between 200 and 350 cells/mm$^3$.

Data included: use and costs of ART and other medications, laboratory tests, outpatient visits, radiographic studies, procedures and hospital services.

Among 816 participants enrolled between 2005 and 2008, the authors determined cost for each year of life saved including patient and caregiver costs, with a median of 21 months and a maximum of three years of follow-up.

During the trial mean total costs for each patient in the early arm were US$1,381 and US$1,033 for standard ART. When research-related costs were excluded and clinical benefit not taken into account, the costs were US$1,158 and US$979, respectively.

While early ART had higher mean ART costs (US$398 compared to US$81), those in the standard arm had higher costs for HIV physician visits, other medications, CD4 cell counts, clinically indicated laboratory tests and radiographs (US$275 compared to US$384).

The authors note that HIV treatment protocols, laboratory tests and medications costs are similar to those used in other resource-poor settings, and in particular those funded in part by PEPFAR. Their findings, they argue, can be generalised to non-trial settings since medical services including nurse and physician contact were comparable at GHESKIO.

The authors note that the cost-effective ratios are conservative and biased against early ART; the clinical benefits of early ART that extend beyond the three years are not taken into account.
Baseline median CD4 cell counts for the early arm compared to the standard arm at the start of ART were 280 cells/mm³ and 166 cells/mm³, respectively.

Studies have shown higher baseline CD4 counts are associated with better immunological recovery and lower mortality and conversely baseline counts under 200 are linked to higher rates of death and disease, including tuberculosis.

The authors note their findings are comparable to results from computer-simulation models in South Africa and Morocco.

The authors conclude starting ART “in HIV-infected adults with CD4 counts between 200 and 350 cells/mm³ in Haiti is cost-effective after excluding laboratory monitoring and clinical benefit. Financial and operational resources should be prioritised so that resource poor countries [can put the new WHO guidelines into practice].”

Reference

Rapid Testing Sharply Cuts HIV Patient Dropout Rate
PBS.org, (09.26.2011) Talea Miller
The proportion of HIV patients lost to follow-up before the initiation of antiretroviral (ARV) therapy “can exceed 50 percent in low-income settings, and is a challenge to the scale-up of treatment,” according to the authors of a new study. This proportion, however, was dramatically reduced after the introduction of rapid CD4 test kits.

“Before the introduction of point-of-care CD4 tests, to obtain a CD4 result involved several steps, each with delays,” wrote the authors from the Mozambique Instituto Nacional de Saúde and the Clinton Health Access Initiative. On average, the process took 10 days. Considering that many patients must walk long distances to reach a health care facility, each additional clinic visit is seen as a barrier to remaining in care.

After the introduction of CD4 rapid test kits, the proportion of patients lost to follow-up before completion of CD4 staging dropped from 57 percent to 21 percent. Total loss to follow-up before ARV treatment was started dropped from 64 percent to 33 percent. The proportion of enrolled patients who began ARV treatment grew from 12 percent to 22 percent, while the median time from enrollment to beginning treatment fell from 48 days to 20 days, chiefly because the median time to complete CD4 staging decreased from 32 days to 3 days.

“Point-of-care CD4 testing enabled clinics to stage patients rapidly onsite after enrollment, which reduced opportunities for pretreatment loss to follow-up,” the authors concluded. “As a result, more patients were identified as eligible for and initiated [ARV] treatment. Point-of-care testing might therefore be an effective intervention to reduce pretreatment loss to follow-up.”

The study, “Effect of Point-of-Care CD4 Cell Count Tests on Retention of Patients and Rates of Antiretroviral Therapy Initiation in Primary Health Clinics: An Observational Cohort Study,” was published early online in the Lancet (2011; doi:10.1016/S0140-6736(11)61052-0).

IRIN Examines Rise In New Leprosy Cases In Remote Region Of Madagascar
IRIN examines an increase in new leprosy cases in Antalaha, a once-prosperous vanilla-exporting town in a remote region of Madagascar, where a 2009 military-supported coup brought the suspension of some foreign aid and trade benefits. The news service writes, "While people are becoming poorer and more susceptible to illness, the public health care system is receiving less money from the government."

"Six to 12 months of treatment with multidrug therapy—a combination of two antibiotics and an anti-inflammatory (medicines that WHO distributes for free)—stops the disease from spreading, but there are other obstacles to overcome," the news service reports, such as a declaration by Malagasy authorities in 2010 that leprosy had been eradicated from the country; the country's tropical climate, which makes diagnosing the illness difficult because it causes many dermatological problems; the fact that many leprosy patients need care for the rest of their lives; and the need for bandages to dress wounds, which are often lacking in health centers (9/26).

Aborigines Have Higher STD Rates Than General Australian Population
Aborigines in Australia have higher rates of sexually transmitted diseases such as gonorrhea, syphilis, and chlamydia than the country's general population, according to research by the University of New South
Wales' Kirby Institute and reported on Tuesday at a sexual health conference, the Associated Press/Seattle Times reports.

James Ward, head of the Kirby Institute's indigenous health program, "noted the Aboriginal population is far younger than the Australian average and STDs disproportionately infect younger people," the news agency writes, adding he "said Aborigines also lacked knowledge about STDs and health workers often focused on more pressing health needs in their disease-ravaged communities." Ward also said reaching the population with health campaigns was difficult because many live in remote areas of the Outback, according to the AP. However, he noted he felt an effort to hang decorated canisters filled with condoms on trees where people can procure them anonymously is working, the AP states (McGuirk, 9/26).

MVA-B Spanish HIV vaccine shows 90 percent immune response in humans

Phase I clinical trials developed by Spanish Superior Scientific Research Council (CSIC) together with Gregorio Marañón Hospital in Madrid and Clínica Hospital in Barcelona, reveals MVA-B preventive vaccine's immune efficiency against Human's immunodeficiency virus (HIV). 90% of the volunteers who went through the tests developed an immunological response against the virus and 85% has kept this response for at least one year. Safety and efficiency of this treatment have been described in articles for Vaccine and Journal of Virology science magazines.

The success of this vaccine, CSIC's patent, is based on the capability of human's immune system to learn how to react over time against virus particles and infected cells. "MVA-B vaccine has proven to be as powerful as any other vaccine currently being studied, or even more", says Mariano Esteban, head researcher from CSIC's National Biotech Centre.

In 2008, MVA-B already showed very high efficiency in mice as well as macaque monkeys against Simian's immunodeficiency virus (SIV). Due to its high immunological response in humans, Phase I clinic trials will be conducted with HIV infected volunteers, to test its efficiency as a therapeutic vaccine.

Weapon's origins

Back in 1999, Esteban's research team began to work in the development and preclinical studies of MVA-B, which name comes from its composition, based in Modified Ankara Vaccinia virus. MVA-B is an attenuated virus, which has already been used in the past to eradicate smallpox, and also as a model in the research of many other vaccines. The "B" stands for the HIV subtype it is meant to work against, the most common in Europe.

Development of MVA-B is based in the insertion of four HIV genes (Gag, Pol, Nef & Env) in Vaccinia's genetic sequence. A healthy immunitary system is able to react against MVA. On the other hand, the inserted HIV genes in its DNA are not able to self-replicate, which guarantees the safety of the clinical trial.

30 healthy volunteers participated in this clinical trial. 24 of them were treated with MVA-B, while the other 6 were treated with a placebo, following a double-blind testing method. 3 doses of the vaccine were given via intramuscular route in weeks 0, 4 and 16. The effects were studied in peripheral blood until the trial ended on week 48.

Combat battalion

Inoculating the vaccine in a healthy volunteer is intended to train it's immune system to detect and learn how to combat those virus components. According to Esteban " it is like showing a picture of the HIV so that it is able to recognise it if it sees it again in the future".

Lymphocytes T and B are the main cells in this experiment, the soldiers in charge of detecting the foreign substances in the body and sending the right coordinates to destroy them.

"Our body is full of lymphocytes, each of them programmed to fight against a different pathogen" says Esteban. For that reason "Training is needed when it involves a pathogen, like the HIV one, which cannot be naturally defeated".

Lymphocytes B are responsible for the humoral immune response, producing antibodies which attack the HIV particles before they penetrate and infect the cell, anchoring themselves to the external structure
and blocking it. 48th week blood tests reveal 72.7% of the treated volunteers hold specific antibodies against HIV.

On the other side, lymphocytes T control cell’s immune response, in charge of detecting and destroying HIV infected cells. In order to verify their defence response to the vaccine, production of interferon gamma immunitary protein was measured.

Tests performed on the 48th week, 32 weeks after the last inoculation of the vaccine, show the production of lymphocytes T CD4+ and CD8+ of the vaccinated group is 38.5% and 69.2%, respectively, while it stays at 0% in the control group.

**Action in several fronts**

Besides interferon gamma, other immune proteins (cytokines and chemokines) are produced by the body when the presence of a pathogen is detected. Each of these proteins tends to attack a different enemy front. When T lymphocytes’ defence action is able to generate several of these proteins it is called a polyfunctional action. CSIC’s researcher adds "The importance of polyfunctionality has to do with the capability of pathogens to develop resistance to the immune systems attacks. The higher the polyfunctionality, the lower the resistance".

The defence spectrum of T lymphocytes in vaccinated subjects was measured based on the production of 3 other immunitary proteins. Tests indicate the vaccine generates up to 15 types of lymphocyte T CD4+ and CD8+ populations. 25% of CD4+ type and 45% of CD8+ type are able to produce two or more different proteins, proving their polyfunctionality.

**War veterans**

For a vaccine to become really effective, besides its immune system’s defence capability, generating a long lasting response against future attacks is the key. For this purpose, the body needs to be able to keep a basic level of memory T lymphocytes. These lymphocytes, generated after a first pathogen attack, are veteran soldiers, which can circulate the body for years, prepared to respond to a new enemy’s incursion.

48th week blood tests ran on vaccinated subjects show over 50% of CD4+ and CD8+ lymphocytes were memory T lymphocytes in the 85% of the patients who kept an immune response at this point of the trials.

In Esteban’s opinión "MVA-B immune profile meets, initially, the requirements for a promising HIV vaccine". MVA-B is not capable of removing the virus from the body as once a cell is infected, virus’ genetic data is integrated and replicated with the cell. However, the immune response induced by the vaccine could keep the virus under control, “if the virus enters the body and tries to develop in a cell, the immune system is ready to inactivate the virus and destroy the infected cell”.

According to CSIC’s researcher: "If this genetic cocktail passes Phase II and Phase III future clinic trials, and makes it into production, in the future HIV could be compared to herpes virus nowadays”. Virus would not cause a disease anymore and would become a minor chronic infection, which would only show its effects in a low defence scenario, with a much lower contagious profile.

**Hide-and-seek: Altered HIV can’t evade immune system ***

Researchers at Johns Hopkins have modified HIV in a way that makes it no longer able to suppress the immune system. Their work, they say in a report published online September 19 in the journal Blood, could remove a major hurdle in HIV vaccine development and lead to new treatments.

"Something about the HIV virus turns down the immune response, rather than triggering it, making it a tough target for vaccine development," says David Graham, Ph.D., assistant professor of molecular and comparative pathobiology and medicine. "We now seem to have a way to sidestep this barrier," he adds.

Typically, when the body’s immune system cells encounter a virus, they send out an alarm by releasing chemicals called interferons to alert the rest of the body to the presence of a viral infection. When the immune cells encounter HIV, however, they release too many interferons, become overwhelmed and shut down the subsequent virus-fighting response.

The researchers had learned from other studies that when human immune cells (white blood cells) are deplete of cholesterol, HIV can no longer infect them. It turns out the coat that surrounds and protects the HIV viral genome also is rich in cholesterol, leading the Johns Hopkins team to test whether viruses lacking cholesterol could still infect cells at all.

The researchers treated HIV with a chemical to remove cholesterol from the viral coat. Then they introduced either the cholesterol-diminished or normal HIV to human immune cells growing in culture dishes, and measured how the cells responded. The cells exposed to cholesterol-diminished HIV didn’t release any initial-response interferons, whereas the cells exposed to normal HIV did.
"The altered HIV doesn't overwhelm the system and instead triggers the innate immune response to kick in, like it does with any first virus encounter," says Graham.

Next, the researchers checked to see if cholesterol-diminished HIV activates so-called adaptive immune responses—the responses that help the body remember specific pathogens long-term so the body develops immunity and counters future infections. To do this, they put normal HIV or cholesterol-diminished HIV into blood samples, which contain all the different cells needed for an adaptive immune response.

More specifically, they tested blood samples from people with previous exposure to HIV in order to see if their blood could mount an adaptive immune response. Blood samples were used from 10 HIV positive people and from 10 people repeatedly exposed to HIV who weren't infected. The researchers didn't expect the HIV-positive blood to respond to either version of HIV because of the severely damaged immune systems of HIV patients. However, when cholesterol-diminished HIV was introduced to the non-infected HIV blood in a tube, the cells of the adaptive immune response reacted against the virus. By altering the virus, explains Graham, the researchers were able to reawaken the immune system's response against HIV and negate HIV's immunosuppressive properties.

"In addition to vaccine applications, this study opens the door to developing drugs that attack the HIV viral coat as an adjunct therapy to promote immune system detection of the virus," says Graham.

Expert panel picks `best buys` for HIV prevention
Keith Alcorn
Published: 29 September 2011
If $10 billion of new money can be spent on HIV prevention over the next five years, the priorities should be more investment in vaccine research, mass infant circumcision, preventing mother to child transmission, safer blood supplies and a scale up of antiretroviral treatment, according to a panel of five of the world's most distinguished economists.

Their recommendations, released on 28 September, are the product of a review process managed by the Copenhagen Consensus Center, a think-tank funded by the Danish government to evaluate the most effective solutions to global development problems.

Investing in vaccine research and development
Overall, the panel found this to be the most compelling investment. “It is likely that spending an extra $100 million a year on vaccine research will meaningfully shorten the time in which a vaccine is developed,” the panel noted.

Although a vaccine is found to be highly cost-effective in itself, it is the speeding up of vaccine research by spending a relatively small amount over the next five years that makes it the panel’s `best buy`. Having a vaccine in 2030 rather than 2040 would save around $100 billion according to the most conservative calculation, which doesn't factor in the gains in productivity that could be achieved by infections averted.

Introduce medical infant male circumcision
Circumcising all male infants in countries with a high HIV burden, at a cost of $3.15 billion over five years, would be a better investment than campaigns for adult male circumcision. This is partly because the panel feared that circumcision campaigns will lead men to have more unprotected sex in the long run because they feel less vulnerable to infection. It is worth noting that five-year follow-up of men who took part in the first major randomised trial of circumcision for HIV prevention found no evidence of an increase in risky sex.

Prevention of mother-to-child transmission
A scale-up of interventions to prevent mother-to-child transmission would be highly cost-effective, but also remarkably cheap – just $140 million over five years to avert an estimated 265,000 infections. The potential costs averted could be as high as $32 billion. The challenge in making this investment lies in improving access to services and reducing the stigma of HIV diagnosis, noted Lori Bollinger of the Futures Institute in a paper analysing the cost-effectiveness of interventions to prevent non-sexual HIV transmission.

Improving safety of the blood supply
The cheapest and most cost-effective intervention recommended by the panel is making blood transfusions safer by ensuring that all countries have a high-quality system for screening blood donations. An investment of $2 million over 5 years could avert around 150,000 new infections and would benefit nearly half a billion people who live in countries with unsound screening systems.
Maximising treatment coverage in people with low CD4 counts
The panel concluded that maximising treatment coverage for people with low CD4 counts by spending an extra $6.2 billion over five years would have the biggest impact on new infections, but only if it was accompanied by comprehensive prevention activities. Mead Over and Professor Geoff Garnett of Imperial College, London, who carried out the modelling on treatment, said that neither treatment nor prevention alone would have sufficient impact on new infections.

They say that their modelling suggests that economic growth after 2020 will allow many more African countries to follow the lead of South Africa and Botswana in taking responsibility for their HIV treatment costs, suggesting that an early investment could reap long-term rewards.

Other measures
Measures which proved less attractive to the panel, but which are still cost-effective, include:

- Cash transfers to keep girls in school: although a sound policy choice, the HIV-related benefit of this expenditure would be quite limited.
- Reducing risky drug injecting behaviours: although cost-effective, the impact is likely to be limited in sub-Saharan Africa in comparison to investments in blood safety or prevention of mother-to-child transmission.

Further information
Detailed research papers and further information on the Rethink HIV project is available at the Rethink HIV website.

Tenofovir PrEP arm dropped in women's HIV prevention trial ***
Keith Alcorn
Published: 29 September 2011
A major HIV prevention trial comparing a tenofovir microbicide with two forms of oral pre-exposure prophylaxis as HIV prevention methods for women is to halt investigation of oral tenofovir pre-exposure prophylaxis, the Microbicide Trials Network announced on Wednesday.

The decision was taken after the independent Data and Safety Monitoring Board for the VOICE study concluded that even if the trial ran to its planned conclusion, it would be impossible to demonstrate any significant difference in effect between oral tenofovir and a dummy pill (a placebo) in preventing new HIV infections.

The VOICE trial (Vaginal and Oral Interventions to Control the Epidemic) was designed to compare tenofovir microbicide gel, oral tenofovir pre-exposure prophylaxis and oral pre-exposure prophylaxis using the tenofovir / emtricitabine combination pill Truvada. The study also contains two placebo arms: a placebo gel arm and a placebo tablet arm.

VOICE has recruited 5,029 women at 15 trial sites in Uganda, South Africa and Zimbabwe. About 1,000 women will stop taking tenofovir in the study. The trial will continue to test tenofovir microbicide gel and Truvada, and women who are receiving oral tenofovir will be informed of the need to stop taking the drug at their next scheduled study visit.

Final results from the study are expected in early 2013, after all participants have completed at least one year of follow-up.

"Of course we are disappointed to hear that the tenofovir pill arm of VOICE will not be able to answer the question of whether or not the drug prevents HIV infection in women in this study," said Mitchell Warren, AVAC Executive Director.

"This development raises as many questions as answers about how oral pre-exposure prophylaxis, or PrEP, might work for women, making the continuation of the VOICE study, along with other research for new HIV prevention options for women, as essential as ever," Warren added.

Yasmin Halima, Director of the Global Campaign for Microbicides, stressed the value of VOICE.

"With the good news that PrEP has been shown in studies to reduce HIV risk in men who have sex with men, serodiscordant couples, and sexually active heterosexual men and women, the key question remains—do we have sufficient evidence that PrEP works in women? For this reason, VOICE continues to be an exceptionally important study.

"Not only does it include both oral PrEP and a vaginal microbicide in the same trial, but VOICE, we hope, will help provide the evidence we need to bring us closer to delivering two more options for women."

Tenofovir-only PrEP was shown to be effective by the Partners study, which announced results in July 2011. That study compared pre-exposure prophylaxis with either tenofovir or Truvada with a placebo arm, and found that the risk of infection was reduced by 62% in the tenofovir arm and by 73% in the Truvada
arm. The difference between the two active drugs was not significant. That study recruited both men and women.

Another study, conducted only in women, has shown a lack of effect of PrEP using Truvada. The FEM PREP study was halted in April 2011 after the study’s Data and Safety Monitoring Board concluded that the trial would be unable to show a preventive effect of Truvada PrEP even if it ran to its planned conclusion.

On the other hand the TDF-2 study, which recruited both men and women in Botswana, has shown that Truvada reduced the risk of infection by 63%. The study was not designed to evaluate whether Truvada was equally effective at preventing infection for men and for women. Results from the TDF-2 study were announced in July 2011.

**HIV vaccine is a small breakthrough, but not a cure**

Tests produced encouraging results for researchers in Spain, but the eradication of this disease is still a long way off.

*Will Harris, guardian.co.uk*, Thursday 29 September 2011 11.52 EDT

**What is this vaccine?**

Scientists at two Spanish hospitals have identified a vaccine they claim could one day dramatically reduce the effect of HIV on the human body. The vaccine, known as MVA-B, is a variation on the same vaccinia virus that was used to eradicate smallpox in the mid-20th century. The virus, which most immune systems can neutralise easily, was manipulated to carry four HIV genes, then given to 24 healthy individuals to gauge how their immune systems would respond. Around 90% of volunteers on the trial developed an immune response against HIV, while 85% are still showing this response a year since vaccination.

**How would it work?**

MVA-B is a therapeutic vaccine, which means – if refined to the point where it was totally effective – it would be administered only to those already living with HIV. It would then control the virus in their bodies in much the same way modern antiretroviral treatments do, except people would only need a single injection (or annual jab) rather than a daily regime of tablets. Such a vaccination programme, rolled out globally, would not only improve the health of the millions living with HIV worldwide, it would also have a significant impact in reducing onward HIV transmission.

**Is it truly a breakthrough?**

Yes, but a small one. Anything that helps us better understand HIV and how it works is certainly good news. However, it’s important to remember this was a phase I trial, working with a very small cohort of volunteers (in comparison, a 2009 trial by the US army and Thai government saw an experimental vaccine given to over 8,000 people). HIV is an incredibly complex virus, with many different strains that we are still learning about. This study, which only looked at one strain, really is just one step on a longer journey.

**What other treatments are currently being researched?**

Therapeutic vaccines are an exciting area of research, but there are still lots of avenues to explore. Right now, in thousands of labs all over the world, a small army of scientists and researchers are looking at different ways we might one day eradicate HIV, just as we have done with other epidemics. Other approaches showing promise include gene therapy and treatment as prevention (offering antiretroviral drugs to people who are HIV-negative but regularly take risks with their sexual health).

**How far away from an effective vaccine are we?**

The short answer is we don't know. Scientists are making new discoveries all the time; we know that some will be the foundation of an eventual cure, while others will fall by the wayside. For the time being, we all have a responsibility to try and minimise the epidemic's spread. So long as there’s no vaccine and no cure, the best way to protect yourself against HIV and other STIs is to use condoms when having sex.

**Economists Say Adult Circumcision Not Best Anti-HIV Tactic**

*USA Today*, (09.28.2011)  Oren Dorell

A cost-benefit analysis of HIV/AIDS investments in sub-Saharan Africa suggests that more resources should be channeled toward vaccine research, an expert panel of economists reported Wednesday. The study, conducted by the panel for Denmark’s state-funded Copenhagen Consensus Center (CCC), evaluated the costs of various interventions per lives saved.
Adult male circumcision can reduce the risk of female-to-male HIV transmission by about 60 percent. But increasing annual AIDS vaccine spending would be a better investment because it could potentially eradicate the disease, said Bjorn Lomborg, CCC’s director.

Preventing mother-to-child HIV transmission, promoting infant male circumcision, and improving blood supply safety also would be high-value investments, the panel said. These interventions “are so cheap and effective” they leap to the top of cost-effective interventions, Lomborg said.

While the World Bank and US State Department support adult male circumcision to prevent HIV, Lomborg said the effort would require “a large public campaign to get people into the clinic.” Recruiting volunteers would not be easy, and “it could cause more risky behavior,” he said.

However, adult male circumcision could be likened to a vaccine, since it cuts infection risk by 60 percent, said Marelie Gorgens, HIV prevention coordinator at the World Bank, who disagrees with the economists. “We need to spend money on things we know work,” Gorgens said.


**Drugs to Curb a Deadly Inheritance**

*New York Times*, (09.27.2011) Nicholas Bakalar

Lesotho, where 23 percent of the population are HIV-positive, is working with UNICEF and the Global Fund to Fight AIDS, TB and Malaria to test three versions of the “Mother–Baby Pack” for HIV prevention and treatment. Since January, more than 14,000 test packs have been distributed.

When a pregnant woman visits a health clinic and is found to be HIV-positive with a CD4 count above 350, she is given a pack containing the antiretroviral AZT, to be taken starting at 14 weeks of pregnancy. The pack also includes nevirapine for the baby, to be given from birth until the infant is six weeks old.

For HIV-positive mothers with a CD4 count below 350, the pack includes the same medicine and dosing schedule for the baby, along with three, and sometimes four, antiretrovirals for the mother. A third pack, for women who do not have HIV, contains only nutritional supplements.

All the packs have an instructional pamphlet in the local language, Sesotho, and the packages are color-coded to show which drugs to take and when. Pictures are included for women who cannot read.

Some health experts question whether the packs could do more harm than good, since having seven months of medicines could make pregnant women less likely to seek prenatal care. There also is a chance the drugs could be misused and lead to resistance, or that stigma could cause some women to shun the packs.

“We are about to evaluate the program and will be able to objectively respond on the impact,” said Dr. Mpolai M. Moteetee, Lesotho’s director-general of health services. At that point, officials will know “how well the pack is received, the mothers’ capacity to use the medicines properly, and whether it is aiding in proper treatment.”

**Rutgers, UMDNJ Research Provides Unprecedented Insight into Fighting Viruses**

Researchers at Rutgers and UMDNJ-Robert Wood Johnson Medical School have determined the structure of a protein that is the first line of defense in fighting viral infections including influenza, hepatitis C, West Nile, rabies, and measles.

Principal investigators of the study, “Structural basis of RNA recognition and activation by innate immune receptor RIG-I,” chosen for advanced online publication in *Nature*, say the research is key in the development of broad-based drug therapies to combat viral infections.

“Understanding innate immunity to viral infections is crucial to developing drugs that can fight viruses or control inflammation,” said Joseph Marcotrigiano, assistant professor of chemistry and chemical biology at Rutgers who along with Smita Patel, professor of biochemistry at Robert Wood Johnson Medical School, are principal investigators on the newly released study. “Having this foundation is extremely important.”

RIG-I is a receptor protein that recognizes differences in molecular patterns in order to differentiate viral RNA – the process during which virus particles makes new copies
of themselves within a host cell and can then infect other cells – from cellular RNA. What researchers discovered is that viral RNA, as opposed to single-stranded cellular RNA, is a double-stranded structure. This double-stranded difference is the reason the RIG-I protein recognizes it and initiates a signal to induce anti-immune and anti-inflammatory defenses within the cell.

Prior to this research, there was little understanding on how RIG-I protein recognized the viral infections, said Patel. Knowing that it is due to the double-stranded molecular structure of the viral RNA is critical because, he said, "a failure of RIG-I to identify viral RNA can lead to alterations of the cell, including cell death, inflammation, autoimmune diseases, and cancer."

This is a first step, the scientists say, in helping to develop therapies that interfere with a broad variety of viral infections – a major breakthrough for millions of people who get sick from viruses which cannot be treated effectively by current medication.

"This work provides unprecedented insights on the molecular mechanism of viral RNA recognition by RIG-I," said Barbara Gerratana, who oversees enzyme catalysis grants at the National Institute of General Medical Sciences of the National Institutes of Health. "As a result, we have a deeper understanding of how the human body fights viral infections and a structural basis of the development of new anti-viral therapeutics."

**Correcting Sickle Cell Disease With Stem Cells**
ScienceDaily (Sep. 29, 2011) — Using a patient’s own stem cells, researchers at Johns Hopkins have corrected the genetic alteration that causes sickle cell disease (SCD), a painful, disabling inherited blood disorder that affects mostly African-Americans. The corrected stem cells were coaxed into immature red blood cells in a test tube that then turned on a normal version of the gene.

The research team cautions that the work, done only in the laboratory, is years away from clinical use in patients, but should provide tools for developing gene therapies for SCD and a variety of other blood disorders.

In an article published online August 31 in Blood, the researchers say they are one step closer to developing a feasible cure or long-term treatment option for patients with SCD, which is caused by a single DNA letter change in the gene for adult hemoglobin, the principle protein in red blood cells needed to carry oxygen. People who inherited two copies—one from each parent—of the genetic alteration, the red blood cells are sickle-shaped, rather than round. The misshapen red blood cells clog blood vessels, leading to pain, fatigue, infections, organ damage and premature death.

Although there are drugs and painkillers that control SCD symptoms, the only known cure—achieved rarely—has been bone marrow transplant. But because the vast majority of SCD patients are African-American and few African-Americans have registered in the bone marrow registry, it has been difficult to find compatible donors, says Linzhao Cheng, Ph.D., a professor of medicine and associate director for basic research in the Division of Hematology and also a member of the Johns Hopkins Institute for Cell Engineering. "We're now one step closer to developing a combination cell and gene therapy method that will allow us to use patients' own cells to treat them."

Using one adult patient at The Johns Hopkins Hospital as their first case, the researchers first isolated the patient's bone marrow cells. After generating induced pluripotent stem (iPS) cells—adult cells that have been reprogrammed to behave like embryonic stem cells—from the bone marrow cells, they put one normal copy of the hemoglobin gene in place of the defective one using genetic engineering techniques. The researchers sequenced the DNA from 300 different samples of iPS cells to identify those that contained correct copies of the hemoglobin gene and found four. Three of these iPS cell lines didn't pass muster in subsequent tests.

"The beauty of iPS cells is that we can grow a lot of them and then coax them into becoming cells of any kind, including red blood cells," Cheng said. In their process, his team converted the corrected iPS cells into immature red blood cells by giving them growth factors. Further testing showed that the normal hemoglobin gene was turned on properly in these cells, although at less than half of normal levels. "We think these immature red blood cells still behave like embryonic cells and as a result are unable to turn on high enough levels of the adult hemoglobin gene," explains Cheng. "We next have to learn how to properly convert these cells into mature red blood cells."

Only one drug treatment has been approved by the FDA for treatment of SCD, hydroxyurea, whose use was pioneered by George Dover, M.D., the chief of pediatrics at the Johns Hopkins Children's Center. Outside of bone marrow transplants, frequent blood transfusions and narcotics can control acute episodes.

Journal Reference: