September 2012 Epidemics and AIDS Update

1. Far From 'Junk,' DNA Dark Matter Plays Crucial Role
2. Killer Silk
3. Drinking Better Bacteria
4. Getting to Know the Genome ****
5. Vaginal Ring Protects Monkeys Against AIDS Virus, Study Shows
6. South Africa: When Sex Is Work
7. Reclaiming HIV as a 'Gay' Disease
8. Protein Critical to Gut Lining Repair Identified
9. High rate of infections in people with HIV receiving Bio-Alcamid treatment for facial lipoatrophy
10. Analysis: Use of pill to prevent HIV may be limited in U.S
11. Maryland man faces rarely used HIV transmission charges
12. RV144 vaccine efficacy increased against certain HIV viruses
13. AIDS Spreading Fast Across East Europe
14. Most Asian Countries Fail To Include Rotavirus Vaccine In National Immunization Programs Citing Cost As Barrier
15. Success And Failure In Fighting Cholera In Haiti
16. Middle-aged people with HIV have a high risk of falls
17. Double trouble: daily function and the impact of old age and HIV
18. AIDS Vaccine Sleuths Find New Clues as 30-Year Hunt Continues
19. Oxyphenbutazone can kill drug resistant TB
20. UCLA stem cell researchers use gene therapy to restore immune systems in 'bubble babies'
21. Reconstructed 1918 influenza virus has yielded key insights, scientists say
22. Gladstone scientists develop technique to decipher the dormant AIDS virus concealed in cells
23. Powerful New Method for Finding Therapeutic Antibodies Devised: Technique Hones and Expands the Power of Large Numbers
24. Designer invents condom cover that can be opened with flick of a thumb
25. IPS Examines Controversy Over WHO-Approved Drug To Prevent Hemorrhage After Labor
26. Gut bacteria increase fat absorption
27. Sinusitis linked to microbial diversity
28. 'Berlin Man,' Doctor Convinced HIV Cure Is Real
29. Booster HIV Drug Can Be Dropped
30. Long-Lasting HIV Drug Could Change Therapy
31. New analysis in Science tells how world eradicated deadliest cattle plague
32. Immune system compensates for 'leaky gut' in inflammatory bowel disease susceptibility
33. Laser-powered 'needle' promises pain-free injections
34. Mutation Breaks HIV's Resistance to Drugs, Says MU Researcher ***
35. Study of Giant Viruses Shakes Up Tree of Life
36. Flu Fights Dirty
37. Rethinking Herbal Medicine
38. Ebola Outbreak In DRC Responsible For As Many As 31 Deaths, According To Revised Count
39. Some Guinean Residents Seek Cholera Vaccine; Outbreak In Sierra Leone Winding Down
40. Floods, Cholera In Niger Have Claimed 162 Lives Since July, OCHA Reports
41. X-Rays Reveal the Self-Defence Mechanisms of Bacteria
42. 'Siloed' Agencies Hindered in Efforts to Fight Animal-To-Human Diseases, Analysis Finds
43. HIV infection doesn't generally affect the response to syphilis treatment
44. Navajo Nation Reports HIV/AIDS Increases
45. Prisoner in African Jail Sues to Get HIV Meds
46. Number Of Recorded Dengue Cases Up 36% Over Last Year In Costa Rica
47. Man Gets 30 Years in Hepatitis C Case
48. Viruses not to blame for chronic fatigue syndrome after all
49. New Findings on Protein Misfolding
50. International Medical Corps Responding to Hepatitis E Outbreak in South Sudan
51. Bishop Stands Firm Against STD Vaccine in Catholic Schools Despite Lawsuit Threat
52. WHO Working With Partners To Stop Ebola From Spreading In DRC
53. WHO Increasing Efforts To Fight Cholera In Sierra Leone
54. Researchers identify possible key to slow progression toward AIDS
Among the many mysteries of human biology is why complex diseases like diabetes, high blood pressure and psychiatric disorders are so difficult to predict and, often, to treat. An equally perplexing puzzle is why one individual gets a disease like cancer or depression, while an identical twin remains perfectly healthy.

Now scientists have discovered a vital clue to unraveling these riddles. The human genome is packed with at least four million gene switches that reside in bits of DNA that once were dismissed as “junk” but that turn out to play critical roles in controlling how cells, organs and other tissues behave. The discovery, considered a major medical and scientific breakthrough, has enormous implications for human health because many complex diseases appear to be caused by tiny changes in hundreds of gene switches.

The findings are the fruit of an immense federal project, involving 440 scientists from 32 labs around the world. As they delved into the “junk” — parts of the DNA that are not actual genes containing instructions for proteins — they discovered it is not junk at all. At least 80 percent of it is active and needed.

The result is an annotated road map of much of this DNA, noting what it is doing and how. It includes the system of switches that, acting like dimmer switches for lights, control which genes are used in a cell and when they are used, and determine, for instance, whether a cell becomes a liver cell or a neuron.

The findings have immediate applications for understanding how alterations in the non-gene parts of DNA contribute to human diseases, which may in turn lead to new drugs. They can also help explain how the environment can affect disease risk. In the case of identical twins, small changes in environmental exposure can slightly alter gene switches, with the result that one twin gets a disease and the other does not.

“It’s Google maps,” said Eric Lander, president and founding director of the Broad Institute of Harvard and the Massachusetts Institute of Technology. Its predecessor, the Human Genome Project, which determined the entire sequence of human DNA, “was like getting a picture of earth from space,” he said. “It doesn’t tell you where the roads are, it doesn’t tell you what traffic is like at what time of the day, it doesn’t tell you where the good restaurants are, or the hospitals or the cities or the rivers.”
The new result “is a stunning resource,” said Dr. Lander, who was not involved in the research that produced it but was a leader in the Human Genome Project. “My head explodes at the amount of data.”

The discoveries were published on Wednesday in six papers in the journal *Nature* and in 24 papers in Genome Research and Genome Biology. In addition, The Journal of Biological Chemistry is publishing six review articles and Science is publishing yet another article.

Human DNA is “a lot more active than we expected, and there are a lot more things happening than we expected,” said Ewan Birney of the European Molecular Biology Laboratory-European Bioinformatics Institute, a lead researcher on the project.

In one of the Nature papers, researchers link the gene switches to a range of human diseases — *multiple sclerosis, lupus, rheumatoid arthritis, Crohn’s disease, celiac disease* — and even to traits like height. In large studies over the past decade, scientists found that minor changes in human DNA sequences increase that risk that a person will get those diseases. But those changes were in the junk, now often referred to as the *dark matter* — they were not changes in genes — and it was not clear what their significance was. The new analysis reveals that a great many of those changes alter gene switches and are highly significant.

“Most of the changes that affect disease don’t lie in the genes themselves; they lie in the switches,” said Michael Snyder, a Stanford University researcher for the project, called *Encode*, for Encyclopedia of DNA Elements.

And that, said Dr. Bradley Bernstein, an Encode researcher at Massachusetts General Hospital, “is a really big deal.” He added, “I don’t think anyone predicted that would be the case.”

The discoveries also can reveal which genetic changes are important in cancer, and why. As they began determining the DNA sequences of cancer cells, researchers realized that most of the thousands of DNA changes in cancer cells are not in genes; they are in the dark matter, the junk. The challenge is to figure out which of those dark matter changes were driving the cancer’s growth.

“These papers are very significant,” said Dr. Mark A. Rubin, a prostate cancer genomics researcher at Weill Cornell Medical College. Dr. Rubin, who was not part of the Encode project, added, “They will definitely have an impact on our medical research on cancer.”

In prostate cancer, for example, his group found mutations in important genes that are not readily attacked by drugs. But Encode, by showing which regions of the dark matter control those genes, gives another way to attack them: — target those controlling switches.

Dr. Rubin, who also used the Google maps analogy, explained: “Now you can follow the roads and see the traffic circulation. That’s exactly the same way we will use these data in cancer research.” Encode provides a road map with traffic patterns for alternate ways to go after cancer genes, he said.

Dr. Bernstein said, “This is a resource, like the human genome, that will drive science forward.”

The system, though, is stunningly complex, with lots of redundancies. Just the idea of so many switches was almost incomprehensible, Dr. Bernstein said.

“People have trouble digesting the number,” he added. “Why would you need to have a million switches to control 21,000 genes?”

There also is a sort of DNA wiring system that is almost inconceivably intricate.

“It is like opening a wiring closet and seeing a *hairball* of wires,” said Mark Gerstein, an Encode researcher from Yale. “We tried to unravel this hairball and make it interpretable.”

There is another sort of hairball as well: the complex three-dimensional structure of DNA. Human DNA is such a long strand — about 10 feet of DNA stuffed into a microscopic nucleus of a cell — that it fits only because it is tightly wound and coiled around itself. When they looked at the three-dimensional structure — the hairball — Encode researchers discovered that small segments of dark-matter DNA are often quite close to genes they control. In the past, when they analyzed only the uncoiled length of DNA, those controlling regions appeared to be far from the genes they affect.

The project began in 2003, as researchers began to appreciate how little they really knew about human DNA. In recent years, some began to find switches in the 99 percent of human DNA that is not genes, but they still could not fully characterize or explain what a vast majority of it was doing.

The thought before the start of the project, said Thomas Gingeras, an Encode researcher from Cold Spring Harbor Laboratory, was that only 5 to 10 percent of the DNA in a human being was actually being used.

The big surprise was not only that almost all of the DNA is used but that a large proportion of it is gene switches. Before Encode, said Dr. John Stamatoynannopoulos, a University of Washington scientist who was part of the project, “if you had said half of the genome and probably more has instructions for turning genes on and off, I don’t think people would have believed you.”
By the time the National Human Genome Research Institute, part of the National Institutes of Health, embarked on Encode, there had been major advances in DNA sequencing and computational biology that made it conceivable to try to understand the dark matter of human DNA. Even so, the data analysis was daunting — the researchers generated 15 trillion bytes of raw data. Analyzing the data required the equivalent of more than 300 years of computer time.

Just organizing the researchers and coordinating the work was an enormous undertaking. Dr. Gerstein, who was one of the project’s leaders, has produced a diagram of the authors with their connections to one another. It looks nearly as complicated as the wiring diagram for the human DNA switches. Now that part of the work is done, and the hundreds of authors have written their papers. “There is literally a flotilla of papers,” Dr. Gerstein said. But, he adds, more work has yet to be done — there are still parts of the genome that have not been figured out.

That, though, is for the next stage of Encode.

Killer Silk
Silk impregnated with bleach may provide a new way to fight the formidable spores of the anthrax bacterium.
By Jef Akst | July 1, 2012

ANTHRAX: A cluster of anthrax bacteria (Bacillus anthracis) in the lung/Photo Researchers, CAMR/A. Barry Dowsett

In mid-September 2001, as the dust was still settling at Ground Zero in Lower Manhattan, several news media offices and two US Senators received letters containing spores of the lethal bacterium Bacillus anthracis. Five people died, and 17 others were infected.

“The anthrax attack of 2001 was unprecedented in US history,” the US Environmental Protection Agency (EPA) wrote in an e-mail to The Scientist. “It was the first use of biological weapons on US soil in modern history.”

The cleanup following these attacks was similarly unprecedented, the agency noted. “[The] EPA had decades of experience conducting emergency responses to hazardous materials and oil spills, but had never responded to a biological weapon such as the preparation used in this attack.” After conferring with the Defense Advanced Research Projects Agency (DARPA), which had researched a variety of decontamination agents, the EPA decided to use gaseous chlorine dioxide—a powerful bleach—to fumigate the affected buildings, which included the US Capitol, the Hart Senate Office Building, multiple US post offices, and the American Media, Inc., facility in Boca Raton, Florida; liquid chlorine dioxide to wipe down surfaces; and a pH-amended bleach for personnel decontamination.

SILK SEEDS: The cocoons of silkworms are used to create silk fibers, which are then treated with bleach to make them antimicrobial.US Air Force
“[Chlorine] bleach is a well-known anthrax spore killer,” Benjamin Tanner, founder and president of Antimicrobial Test Laboratories, a contract microbiology lab that tests surfaces and makes disinfectants and sanitizers, wrote in an e-mail. And not just anthrax—the chemical shows antimicrobial efficacy against a broad spectrum of microorganisms, and is a commonly used as a disinfectant and swimming pool sanitizer. “Everybody uses bleach,” says Rajesh Naik, a bio-materials scientist at the Air Force Research Laboratory—even the US Department of Defense, which uses chlorine dioxide to decontaminate materials and equipment that may have been exposed to infectious microbes.

Given chlorine’s powerful biocidal capabilities, researchers have also started to impregnate fabrics with chlorine compounds known as halamines. For example, one can purchase HaloShield bed sheets, which are designed to bind chlorine molecules from laundry bleach in the wash, providing renewable antimicrobial properties. “The gist of it is that you bleach the fabric to activate the N-halamine (which hangs on loosely to the chlorine), and then when it comes into contact with the microbes it chlorinates them,” Tanner says.

But while in laboratory studies such halamine-impregnated textiles have proven highly effective against “clinically relevant bacteria, such as Escherichia coli and Staphylococcus aureus, these textiles have been less effective in deactivating bacterial spores,” such as those mailed in the 2001 anthrax letters, notes industrial chemist Franco Ferrero of the Politecnico di Torino in Italy.

Recognizing this deficiency, Naik and Matthew Dickerson, a bioengineer in his lab, decided to explore the possibility of bleaching silk, a proteinaceous fiber obtained from the cocoons of mulberry silkworms, larvae of the moth Bombyx mori. Researchers had previously used halamine chemistry to add antimicrobial qualities to Nomex, a derivative of nylon, which itself was “a synthetic answer to silk shortage during the Second World War,” Dickerson says. “So it’s kind of a reverse evolution of technologies—we decided to go backwards in time, looking at a biological material, which has all the appropriate chemistry to add this kind of functionality”—namely, the presence of lots of amino groups to which the chlorine ion can bind.

After about a year of fiddling around with the pH, preparation times, and other details, Dickerson found what Naik calls the “sweet spot,” in which “you’re getting effective loading but not degrading the performance of the material itself.” The procedure, which involved dipping silk swatches in a solution of sodium hypochlorite, a common commercial bleach, for 1 hour, yielded a higher loading of chlorine into the material than had been achieved for Nomex and other fabrics. As a result, the bleached silk killed more than 99.9 percent of colony-forming units of Escherichia coli within 10 minutes, and was also effective against Bacillus thuringiensis spores, which the researchers used as a proxy for the more dangerous Bacillus anthracis.

“It could be a very powerful new technology, born from two tried-and-true materials—silk and bleach,” says Tanner. “Applications are boundless, I think, for such a simple technology.”

And its simplicity does seem to be key. “It didn’t require specialized equipment,” Dickerson notes. “The chemistry is such that—I’m not recommending this, but—someone could probably do it in their kitchen.” One of the paper’s reviewers even called the work “freshman chemistry,” Naik recalls. “That was exactly our point—that this was so easy, it could be implemented very effectively [on a] large scale.”

Naik and Dickerson are currently working with collaborators to test the silk in the field. In addition to bio-defense applications, such as wiping down surfaces following an anthrax attack, the silk could be used to create antimicrobial garments like hospital gowns or doctor’s coats to help thwart the spread of MRSA, a bacterium that is wreaking havoc in hospitals and communities around the globe, says Naik.

**Drinking Better Bacteria**

Researchers analyzing the bacteria in municipal drinking water find simple measures can increase beneficial bacteria while reducing pathogenic strains.

**By Edyta Zielinska | August 9, 2012**

Although most bacteria are removed from drinking water before it reaches our lips, a few strains survive the filtration and chlorination steps. Researchers from the University of Michigan tracked down the sources of bacteria and found that beneficial populations could be selected by slightly changing the acidity of the water.

The main source of bacterial diversity, surprisingly, was the filters designed to remove the organic matter on which bacteria feed. These filters were shown to play a major role in shaping the bacterial community in the drinking water, suggesting that changing how the filters are cleaned could also steer the microbial community toward beneficial bacteria. The results w
**Getting to Know the Genome**

A massive project involving hundreds of scientists suggests that very little—if any—of the human genome is truly non-functional.

By Ed Yong | September 5, 2012

In 2001, the Human Genome Project produced a near-complete readout of the human species’ DNA. But researchers had little idea about how those As, Gs, Cs, and Ts were used, controlled, or organized, much less how they code for a living, breathing human.

That knowledge gap has just got a little smaller. A massive international project called ENCODE, the Encyclopedia of DNA Elements, has cataloged every nucleotide within the genome that does something—which, it turns out, is significantly more than the 1.5 percent of the genome contains actual instructions for making proteins. The research, a 10-year effort by an international team of 442 scientists, shows that the rest of the genome—the non-coding majority—is still rife with “functional elements.”

“The genome is no longer an empty vastness,” said Shyam Prabhakar from the Genome Institute of Singapore, who was not involved in the study. “It is densely packed with peaks and wiggles of biochemical activity.”

“Almost every nucleotide is associated with a function of some sort or another, and we now know where they are, what binds to them, what their associations are, and more,” added Tom Gingeras, one of the studies’ many senior scientists. The results are published today (September 5), in more than 30 papers across many different journals.

Researchers have long recognized that some non-coding DNA probably has a function, and many solid examples have recently come to light. At the same time, people did believe that much of these sequences were, indeed, junk. The ENCODE project suggests otherwise.

The researchers found that many non-coding parts of the human genome contain docking sites where proteins can bind, affecting the expression of both nearby and distant genes. Other non-coding regions are transcribed into RNA molecules that are never translated into proteins. Still others affect how the DNA is folded and packaged. In sum, these regions are not just junk; according to ENCODE’s analysis, 80 percent of the genome has some biochemical function.

The remaining 20 percent may not be junk either, according to Ewan Birney, the project’s Lead Analysis Coordinator. He explains that while ENCODE looked at 147 different types of cells, there are a couple of thousand in total. If other cell types are examined, functions may emerge for the phantom proportion. “It’s likely that 80 percent will go to 100 percent,” Birney said. “We don’t really have any large chunks of redundant DNA. This metaphor of junk isn’t that useful.”

The implications are vast, from redefining what a “gene” is to providing new clues in the quest to understand diseases and how the genome works in three dimensions. “There are nuggets for everyone here,” Prabhakar said. “No matter which piece of the genome we happen to be studying in any particular project, we will benefit from looking up the corresponding ENCODE tracks.”

Of course, there’s still a long way to go, Birney noted. “I think it’s going to take this century to fill in all the details,” he said. “That full reconciliation is going to be this century’s science.”

**By the numbers**

Researchers already knew that 1.5 percent of the genome codes for proteins. ENCODE found that an additional 8.5 percent codes for regions where proteins stick to DNA, presumably regulating gene transcription. And, because ENCODE hasn’t looked at every possible type of cell or every possible protein that sticks to DNA, this figure is likely conservative. Birney estimates that the total proportion of the genome that either creates a protein or sticks to one is around 20 percent.

The rest of the functional elements in the ENCODE analysis cover other classes of sequence that were thought to be essentially functionless, including introns. “The idea that introns are definitely deadweight isn’t true,” said Birney. Even some repetitive sequences—small chunks of DNA that have the ability to copy themselves and are typically viewed as parasites—are likely to be functional, often containing sequences where proteins can bind to influence the activity of nearby genes. Perhaps their spread across the genome represents not the invasion of a parasite, but a way of spreading control. “These parasites can be subverted sometimes,” Birney said.

Birney expects that many skeptics will argue about the exact proportion—the 80 percent of the genome that ENCODE estimates to be doing something—and about the definition of “functional.” But, he said, “no matter how you cut it, we’ve got to get used to the fact that there’s a lot more going on with the genome than we knew.”
What’s in a gene?
The simplistic view of a gene is that it’s a stretch of DNA that is transcribed to make a protein. But with ENCODE’s data, this definition no longer makes sense. There are a lot of transcripts, probably more than anyone had realized, some of which connect two previously unconnected genes. This means that the boundaries for those genes have to widen, and the gaps between them shrink or disappear.

Gingeras says that this “intergenic” space has shrunk by a factor of four. “A region that was once called Gene X is now melded to Gene Y,” he says. With such blurring boundaries, Gingeras thinks that it no longer makes sense to think of a gene as a specific point in the genome, or as its basic unit. Instead, that honor falls to the RNA transcript. “The atom of the genome is the transcript,” says Gingeras. “They are the basic unit that’s affected by mutation and selection.”

New disease leads
For the last decade, geneticists have run a seemingly endless stream of genome-wide association studies (GWAS), and have thrown up a long list of single nucleotide polymorphisms (SNPs) that correlate with the risk of different conditions. The ENCODE team has mapped all of these GWAS-identified SNPs to their data.

The researchers found that just 12 percent of known SNPs lie within protein-coding areas. They also showed that compared to random SNPs, the disease-associated ones are 60 percent more likely to lie within the non-coding but functional regions that ENCODE identified, especially in promoters and enhancers. This suggests that many of these variants are controlling the activity of different genes, and provides many fresh leads for understanding how they affect our risk of disease. “It was one of those too good to be true moments,” said Birney. “Literally, I was in the room [when they got the result] and I went: Yes!”

The ENCODE researchers also found new links between disease-associated SNPs and specific DNA elements. For example, they found five SNPs that increase the risk of Crohn’s disease, and that are recognized by a group of transcription factors called GATA2. “That wasn’t something that the Crohn’s disease biologists had on their radar,” Birney said. “Suddenly we’ve made an unbiased association between a disease and a piece of basic biology.”

“We’re now working with lots of different disease biologists looking at their data sets,” he added. “In some sense, ENCODE is working from the genome out, while GWAS studies are working from disease in.” So far, the team has identified 400 such hotspots that are worth looking into.

The 3-D genome
Writing the genome out as a string of letters invites a common fallacy: that it’s a two-dimensional, linear entity. In reality, DNA is wrapped around proteins called histones like beads on a string. These are then twisted, folded and looped in an intricate three-dimensional way. In this way, distant parts of the genome can actually be physical neighbors, and can affect each other’s activity.

Job Dekker, a bioinformaticist at University of Massachussetts Medical School, used ENCODE data to map these long-range interactions across just 1 percent of the genome in three different types of cell, and discovered more than 1,000 of them. “I like to say that nothing in the genome makes sense, except in 3D,” said Dekker. The availability of the new ENCODE data is “really a teaser for the future of genome science,” he added.

Sharing the data
The new ENCODE results are vast, reported in 30 central papers in Nature, Genome Biology, and Genome Research, as well as a slew of secondary articles in Science, Cell, and others. And all of the data are freely available to the public.

The pages of printed journals are a poor repository for such a vast trove of data, so the ENCODE team have devised a new publishing model. On the ENCODE portal site, readers can pick one of 13 topics of interest, such as enhancer sequences, and follow them in special “threads” that pull out all the relevant paragraphs from the 30 main papers. “Rather than people having to skim read all 30 papers, and working out which ones they want to read, we pull out that thread for you,” Birney said.

The team has also built what they call a Virtual Machine, a downloadable program that includes all the code that the ENCODE scientists used to analyze their data. Any researcher can download almost-raw data and reproduce any of the analyses in the papers by themselves. It’s the ultimate in transparency. “With these really intensive science projects, there has to be a huge amount of trust that data analysts have done things correctly,” said Birney. With the virtual machine, “you can absolutely replay, step by step, what we did to get to the figure. I think it should be the standard for the future.”
Near-perfect adherence needed to suppress cell-associated HIV

Michael Carter
Published: 05 September 2012
Complete adherence to antiretroviral therapy is needed to ensure suppression of cell-associated HIV, investigators from the Netherlands report in the online edition of the *Journal of Infectious Diseases*.

A total of 40 people taking long-term HIV therapy were included in the study, all of whom maintained an undetectable viral load. However, modest non-adherence to treatment was associated with increases in cell-associated virus.

“Patients who do not fail on ART, but are even modestly nonadherent, may still have ongoing low-level residual HIV replication,” comment the authors. “ART only blocks infections of new cells, and not HIV-1 RNA transcription in infected cells.”

They believe their findings could have important clinical implications, and that “full adherence to modern ART” is required to achieve suppression of cell-associated virus.

Adherence – taking all doses of anti-HIV drugs exactly as prescribed – is central to the success of HIV therapy. Poor adherence can lead to inadequate viral suppression in plasma, the emergence of drug resistance and treatment failure.

The level of adherence needed to achieve and maintain viral suppression with early antiretroviral regimens was 95%. However, more potent drugs with long half-lives have since been developed, meaning that an undetectable plasma viral load can be achieved with much lower levels of adherence, possibly as low as 70%.

However, it is unclear if HIV replication is completely suppressed when adherence is less than perfect. Research has focused on changes in plasma viral load. It has not previously addressed the association between adherence and HIV replication in cells.

“We investigated whether residual replication could be promoted by modest nonadherence to ART,” explain the investigators. “We studied the influence of slightly decreased adherence to therapy on the changes in levels of cell-associated viral markers”: unspliced RNA (usRNA) and DNA.

The study population comprised participants enrolled in a long-term study investigating an adherence-support intervention. Adherence was monitored electronically using MEMS (Micro-Electro-Mechanical Systems) technology.

All the participants had regular viral load tests. The virological success of therapy was also assessed by monitoring cell-associated HIV in peripheral blood mononuclear cells (PBMC). These markers were monitored on three occasions at intervals of three to four months.

At the start of the study, the participants had been on successful HIV therapy with undetectable viral load (except for occasional ‘blips’, transient increases in viral load of below 1000 copies/ml) for a median of 46 months. Their median CD4 cell count was 620 cells/mm³.

HIV usRNA was detectable in 76% of samples and HIV DNA in 96%.

These samples were paired with viral load measurements obtained at the same time. Viral load was undetectable in 91% of instances; the other samples were all below 400 copies/ml.

Adherence was monitored one week before measurement of HIV RNA and DNA in PBMC. Most of the participants (58%) had perfect adherence at all three time points; 20% had less-than-perfect adherence when this was first assessed, but achieved 100% adherence at a later time point; and 22% of patients had “poor adherence” – less than 100% without improvement over the course of the study. Participants with less than 100% adherence took a median of 82% of their doses.

None of the participants experienced a rebound in their viral load.

However, the investigators found a clear association between level of adherence and changes in usRNA.

Median usRNA fell in people with 100% adherence, remained unchanged in those with improving adherence and increased in people with poor adherence (comparison optimal vs poor adherence, p = 0.006).

“Poor adherence was associated with a significant longitudinal increase in levels of usRNA, whereas no significant longitudinal trends in usRNA were observed for patients with optimal or improving adherence,” write the investigators. “This indicates that HIV-1 usRNA in PBMC is a viral molecular marker with a significantly better sensitivity to modest changes in adherence than viral RNA in plasma, measured by an assay with a detection limit of 50 copies/ml.”

They believe their results “suggest that constantly optimal adherence to ART may be required life-long.”
The findings could have real clinical significance. Antiretroviral therapy has been associated with significant improvements in prognosis for people with HIV. However, even with such treatment, the life expectancy of HIV-positive people is generally still poorer than that of HIV-negative individuals. The investigators speculate that this could be due to damage caused by residual HIV replication when adherence is less than perfect. “It is plausible that constant low-level virus replication would exert continuous pressure on the immune system and cause additional morbidity as a result of persistent immune activation, inflammation, and immunosenescence.”

The findings of the study could therefore have implications for advice given to people about adherence. “Forgiveness of ART, defined as an ability to maintain complete viral suppression despite imperfect adherence, may require re-evaluation in view of our results,” conclude the authors.

Reference

Vaginal Ring Protects Monkeys Against AIDS Virus, Study Shows
By Simeon Bennett—Sep 5, 2012 2:00 PM ET
A vaginal ring that emits an HIV-fighting drug protected monkeys from getting a version of the AIDS-causing virus, according to a study that suggests the same approach may help women whose partners won’t wear condoms.

Macaques that received the drug-laced rings were 83 percent less likely to become infected with simian HIV than those that got placebo rings, researchers from the New York-based Population Council wrote in a study published today in the journal Science Translational Medicine. Scientists have been trying to develop tools for women that would reduce the risk of contracting HIV. While a 2010 study of a vaginal gel showed it prevented infections in a large trial in Africa, researchers stopped a similar trial in November because it wasn’t working, possibly because the women weren’t using the gel often enough. Rings, similar to those now used for contraception, may avert that problem.

“This proof-of-concept study confirms that the investment in vaginal rings as a delivery system for HIV prevention is paying off,” Naomi Rutenberg, vice president and director of the Population Council’s HIV and AIDS program, said in a statement.

The rings, made either of silicone or ethylene vinyl acetate, released an experimental drug called MIV-150, an antiviral developed originally by Huddinge, Sweden-based Medivir AB (MVIRB) and licensed to the Population Council in 2003. The approach is designed to ward off infection by preventing HIV from gaining a foothold in the body.

The researchers inserted the devices either 24 hours or two weeks before exposing the monkeys to simian HIV, a virus that combines genes from the human and monkey versions of the infection, and removed them immediately before or two weeks after the exposure.

Timing Matters
Among 17 macaques that got the drug rings, two became infected, compared with 11 of 16 animals who got plain rings. While the timing of the insertion didn’t make a difference, animals whose rings were removed just before the exposure were more likely to become infected than those whose rings remained in place. The Population Council is working on a ring that women could leave in place for as long as three months, and that might also prevent other sexually-transmitted diseases and unplanned pregnancies, it said in the statement.

The U.S. National Institutes of Health said in July it’s starting a trial of a ring that may involve almost 3,500 women in five countries.

South Africa: When Sex Is Work
By Sue Valentine, 5 September 2012
Johannesburg, South Africa — Linda is a small, soft-spoken woman. She takes out her passport and in a matter-of-fact voice explains, “This thing reminds me of my journey, from the time my husband died.”

Linda, who asked that her last name not be used, is a provincial media co-ordinator of Sisonke, the South African sex worker movement. She was one of a long list of speakers at South Africa’s first ever, national symposium on sex work held in Johannesburg recently, which brought together officials from the South African National Aids Council, the Department of Health, the United Nations Population Fund (UNFPA) and non-government organizations, including the Sex Worker Education and Advocacy Taskforce (Sweat) and Sisonke.
As Linda told her story, conference delegates sat in rapt silence. Occasional murmurs of empathy rippled through the room as she explained that although she had hoped to finish school and go to university, her family circumstances had prevented it.

"My father was a peasant farmer, he had two wives and we were 15 children," she said of growing up in Zimbabwe. "He did not have enough money to send all of us to school. My mother was the second wife, and so my brothers from the first wife were the ones to go to school. I could only go up to Grade 9."

At the age of 19, Linda married. Her husband was a medic in the Zimbabwean army. Six years after their marriage he was sent on a peacekeeping mission to the Democratic Republic of Congo where he sustained severe head injuries in a plane crash, leading to his death.

"I was only 25," said Linda. "I had two sons. We had a fully equipped seven-room house in the city, but my husband’s family wanted this for themselves. They said I should marry my husband’s brother, because this was according to their culture and tradition."

Linda was adamant that she was not married "to the whole family". The only solution she saw was to leave Zimbabwe for South Africa where she could earn a living and avoid the pressure from her in-laws.

But first, she had to get a passport. "When my husband was still alive he used to say, 'I don’t want you to work for the family. I will work for you and the kids. And I don’t want you to have a travel document, you’ll be here with the family and I will always come back to you.'"

"I had to go against his wishes to get this document," said Linda. "So every time I look at it, I feel like I have broken his wish, as if I was betraying him, but there was nothing I could do because I wanted to support the family."

The following year, Linda applied for a passport. "At that time, things were very difficult in our country. You needed a lot of money to get a travel document—and it took two years. I applied for it in 2006 and I got it in 2008."

"When I came to South Africa, I was dropped in Musina," said Linda. "I didn’t know anyone. I was wondering how I would find someone who wants a domestic worker. I was sitting with my bag next to me, then this truck driver approached me."

In a country where more than five million people are living with HIV, and sex workers account for one in five new HIV infections, public health workers say it is imperative that South Africans engage in a frank and honest conversation about sex work. Surveys in South Africa’s major cities show an HIV prevalence rate of between 44 and 69 percent among sex workers, whereas in the general population the prevalence is around 17 percent.

However, because South Africa criminalises sex work, bringing with it a general stigma, there is little incentive for sex workers to seek out health services at government clinics where they are treated with disdain or worse.

The World Health Organisation identifies three key risks for those involved in sex work:

- Forced sex increases the risk of transmission of HIV due to physical trauma.
- The threat of violence limits the ability of people to negotiate safer sex.
- Disclosure of HIV test results or the disclosure of a person’s HIV status may also entail an increased risk of violence.

Sex workers generally are well-educated when it comes to safer sex and HIV prevention, but their outlaw status puts them in a weak position if they have to argue with clients to persuade them to use condoms. Furthermore, police frequently harass outdoor sex workers—and if women are found to be carrying condoms, the police use this as evidence that they are sex workers.

Under current South African law both sex workers and their clients are guilty of an offence. However, a report by the South African Women’s Legal Centre published in August 2012 that documents the experiences of more than 300 sex workers found that 70 percent experienced some form of abuse at the hands of the police.

This was acknowledged by the deputy minister of police, Makhotso "Maggie" Sotyu, who, in her address to the National Sex Work Symposium said she was moved by the many complaints of police abuse that she had received in a recent meeting with sex workers.

"You can’t let a police officer rape any person, let alone a sex worker," she said, adding that where police used unnecessary force, these incidents should be treated as criminal acts.

While living outside the law makes sex workers more vulnerable to abuse from police, clients and pimps, it also places a burden on the country’s stretched police services. Sex work activists argue that policing the laws that criminalise sex work absorbs significant resources that, given South Africa’s high crime levels, could better be deployed elsewhere.
According to the executive director of Sweat, Sally-Jean Shackleton, "targeting women with low incomes trying to earn money for their families, police are being told to invade privacy, to make impossible judgements and to devote endless time to surveillance. Of course, there are very few convictions, and instead the police feel that such demeaning rules justify their emotional and physical abuse of sex workers, as evidenced by endless stories received by our organisation".

In a tacit acknowledgement of the futility of criminalising sex work, the deputy minister said that sex work was a reality that was "here to stay" and that the South African police had more "serious challenges than running around after sex workers".

The first country in the world that has recognised sex work as a reality to be regulated like all other work is New Zealand, which decriminalised sex work in 2003. In Australia, the state of New South Wales has a similar approach.

In New Zealand, decriminalisation—as distinct from legalisation—resulted in the following changes:

- It was no longer an offence to procure sex, run a brothel, solicit, or to live off the earnings of sex work.
- Registration of sex workers ceased; it was replaced by licensing of people in a position of control over sex workers in a business of three or more workers.
- A ban on people with drug or prostitution convictions working in brothels was removed.

At the same time, harsher penalties were introduced for a number of offences. These included being the client of a sex worker under the age of 18; coercing someone into sex work or keeping them there; and tougher penalties against any sex worker, client or manager who fails to promote safe sex.

According to Tim Barnett, a New Zealand member of parliament who helped champion the legislation change in 2003, "the sky did not fall in".

He argues that both police and sex workers reported a "better relationship", easing the solving of sex work-related crime, without the corruption temptations created by a criminalized environment. There has also been no evidence of an increase in the number of sex workers and brothels, but there have been cases where brothel owners who abuse sex workers and violent clients have been prosecuted.

"Five years after the law was changed, a major statutory review committee, chaired by the former police commissioner and backed up by extensive research, reported in 2008 that the real impact would take many more years but that the law was working as intended," said Barnett in documents he has presented to Sweat.

Those who oppose the decriminalisation option argue that sex work demeans the dignity of women and that options such as the "Swedish model"—which criminalises only the client and outlaws pimps and brothels—are better options.

According to activists in Sweat and Sisonke, these arguments ignore the indignity of poverty and what it means to lack education for work that pays more than a minimum wage, in an environment of high unemployment.

They also argue that South Africa’s current legal framework is not in line with international treaties to which it is a signatory.

For Linda and other sex workers, the issue is simple: "This is how I feed my family. All we want is for our work to be recognised as work."

Volume 19, Issue 5: Election 2012

Reclaiming HIV as a ‘Gay’ Disease
John-Manuel Andriote

EVEN IN THE FIRST DECADE of the now three-decade-long HIV/Aids plague, there was already talk about “the changing face” of the epidemic. We were told that face was getting darker as more people of color were affected, and more feminine as women also were being diagnosed in greater numbers. This generalization is still made today, and even makes headlines.

While it’s true that the proportion of minorities with HIV has risen over the years, the fact is that, since AIDS was first reported among a group of gay men in 1981, gay and bisexual men of all colors continue to account for by far the largest number of those infected with HIV, those at risk for infection, and those living with untreated HIV. Like it or not, hiv/aids in America is still a profoundly “gay” disease.

But you wouldn’t know it if you looked at the agendas and priorities of the nation’s top GLBT political groups. Beginning in the late 1980’s, they effectively handed off hiv/aids to organizations that focus exclusively on this issue. The problem with this strategy is that, without advocacy from our most
influential organizations—advocacy focused specifically on the needs of gay and bisexual men—the issues affecting those most in need are pushed to the margins of the GLBT legislative and political agenda.

The Obama administration’s “2010 National HIV/AIDS Strategy,” the nation’s first attempt in three decades to develop a cohesive strategy to address the epidemic, calls for a much more targeted focus on gay/bi men—and much more involvement by our community organizations in advocating for us. Like millions of other unemployed, underemployed, and uninsured Americans caught in the grips of the Great Recession, these men—and I count myself among them—rely on public programs such as Medicaid and the federal Ryan White Program, which provides assistance with insurance premiums, medications, and support services aimed at keeping them connected to the medical care they need to stay well and reduce the risk of infecting others. They tend not to have the disposable income needed to have clout with the national GLBT political organizations.

With their attention and resources aimed instead at marriage equality—a priority for their educated, affluent (mostly white) supporters—it’s not clear whether these groups will rise again to the challenge of HIV/AIDS in gay America as they once did so brilliantly in the early, terrifying years. A movement about marriage and family may seem to be an easier sell to the American public, but at what cost?

The National Movement Bows Out

The world has changed since Ginny Apuzzo demanded $100 million for AIDS at a Congressional hearing on August 1, 1983. Two years after the first reported cases, total federal spending for the deadly new disease was only $14.5 million. In 2012, the U.S. government spent a total of $27.7 billion to combat HIV.

Washington lobbying was a new experience for gay advocates in the early 80’s. Apuzzo, who became director of the National Gay Task Force in 1982 (the “L word” was added later to make it the ngltf), told me: “What you have to understand is that the gay and lesbian community in 1980 to ’81 had only one experience with lobbying—that was how to get the gay rights bill through. Every session you’d go in and add two or three sponsors, get people to write from home. That’s where this community’s experience was, and it had to turn around on a dime.”

Millions of dollars were raised for AIDS in the 80’s, expanding the budgets, staffs, and visibility of AIDS-focused organizations as well as the national gay and lesbian political groups, particularly the Human Rights Campaign (HRC) and the ngltf. John D’Emilio, a noted historian of the GLBT movement and history professor at the University of Illinois, told me: “AIDS built the gay movement. It shook loose the resources to transform a movement that was small and based almost entirely on volunteer labor into a movement of full-time people who were devoting themselves to this work and getting paid for it.”

But if HRC and ngltf began to look away from HIV/AIDS issues in the late 80’s, this trend accelerated once the HIV-fighting drugs hit the market beginning in 1996. The highly active antiretroviral therapy (haart) made it possible to talk about living with HIV rather than dying from AIDS. Perhaps this shift in priorities was understandable, but it raised the question whether these organizations were serious in their claim that they represented the entire GLBT community. John D’Emilio, who was the first director of ngltf’s Policy Institute in the mid-90’s, admitted that over the past decade, “AIDS has dropped off the face of the gay map. It’s not that national and state organizations do nothing about it, but it’s not a priority. It gets a lot less attention than ‘Don’t Ask, Don’t Tell’ and ENDA [the Employment Non-Discrimination Act], and, in the last few years, marriage.” Commenting on the rise of marriage equality as the paramount issue on the agenda, D’Emilio added: “The lack of access to marriage is not exactly a crisis. But think of the mobilization and energy that has gone into that in the last five to ten years as opposed to an issue in which thousands of people are dying each year. AIDS is much more of a crisis than marriage. Marriage appeals to people who have social and economic status. AIDS hits more strongly people who don’t have economic status.”

I asked HRC’s chief counsel, Brian Moulton, to respond to critics who say that the HRC isn’t advocating strongly enough for the HIV community. He pointed to the group’s ongoing monitoring of the federal appropriations process, “advocating for appropriate funding and opposing restrictions on syringe exchange and other ideologically driven policy decisions.” He said HRC also is working with various organizations to support a new anti-criminalization bill, to remove the organ transplant ban between HIV-positive individuals, and to push the Food and Drug Administration to adopt a blood donation policy that doesn’t categorically exclude gay/bi men. Moulton also shared an issue brief HRC published this year—the only thing on its website specifically mentioning gay/bi men.

To put Moulton’s comments in perspective, he mentioned nothing about advocating for a proportionate share of federal HIV prevention dollars, or about efforts to repeal the pernicious 1987 “Helms Amendment”—named for the late, rabidly anti-gay North Carolina Senator Jesse Helms—that
continues to restrict federal support for the kind of targeted, explicit prevention messages public health experts have called for since 1986.

As for the ngltf, as of July 2012, three slender paragraphs about hiv/aids on their website were still quoting the group’s statement for World AIDS Day 2009. (To be sure, hiv/aids wasn’t the only issue featuring outdated information on their website.) Ngltf’s communications director Inge Sarda-Sorensen said in an e-mail that the Task Force (as it now prefers to be called) is working to implement the Affordable Care Act; to get the federal government to eliminate its policy of no condoms in prison; to advocate for increased data collection efforts to understand the spread of HIV in the transgender and people of color communities; and to continue to address hiv/aids in its annual “Creating Change” training conference in “an array of workshops, sessions and keynotes.”

However, of the hundreds of workshops offered at the January 21–29, 2012, conference in Baltimore, a grand total of only three workshops focused on hiv/aids—which can hardly be called an “array.” In fact, the three workshops—“HIV and Aging: Why HIV and Aging Policy Matters (or Should Matter) to the GLBT Community,” “Meeting the HIV Prevention Needs of Young Black MSM [men who have sex with men] in Baltimore City: A Reflection,” and “Best Practices for Engaging MSM Communities during Black Gay Pride Events”—barely scratch the surface. That Creating Change is considered the premier boot camp for future activists bodes ill for hiv/aids advocacy on behalf of gay/bisexual men—and for GLBT people in general. By not drawing deeply from the “heroic legacy” of gay America’s victories and defeats in the AIDS epidemic, activists who aren’t well grounded in the community’s very recent past lack the depth needed to anchor their efforts to create a just and equal future.

**Still a Gay Disease**

In communities across America, organizations created to serve middle-class gay men with AIDS now struggle to raise funds to serve the lower-income gay/bi men, particularly African-American and Latino men, who today rely on their services. Their traditional donors—middle-class and affluent white gay men—have “moved on” since they can now get their HIV-related medical care from their private physicians.

Rick Siclari, director of Care Resource, the largest HIV service provider in South Florida, told me in a 2010 interview it’s “a whole new world” for middle-class white gay men—even in his city of Miami, with the highest rate of AIDS cases in the country. “White gay men are not giving as much today,” he said. Now the agency is hoping its new clients, many of them black and Latino, will participate in fundraising by giving them the chance to make smaller donations in the five to ten dollar range.

The old ACT UP slogan of “Silence = Death” still holds, if by “silence” we mean withholding of support. This failure of the gay community to help those in need is based on and justified by the (false) belief that HIV is no longer primarily a “gay” problem—simply because of the experience of a non-representative segment of the gay/bisexual male population. And yet, consider the following statistics:

- In Miami-Dade County, white gay and bisexual men accounted for only seventeen percent of the 32,710 AIDS cases reported between 1981 and July 2010, and only 25 percent of the cases just among gay and bisexual men there. Hispanics and black men are almost exactly equal, each at around 41 percent of the city and county’s AIDS cases. All these men together account for 74 percent of the city’s MSM—comprising 54 percent Hispanics and 20 percent African Americans.

- Gay men are sixty times more likely than heterosexual men, and 54 times more likely than all women, to be diagnosed with HIV. Gay men account for 48 percent of the more than one million people living with HIV in the U.S., an estimated 532,000 men (according to the Centers for Disease Control and Prevention, or CDC).

- MSM, including those who inject drugs, constituted 58 percent (24,977) of the estimated 42,959 Americans (31,872 of them males) newly diagnosed in 2009 with HIV infection.

- In 21 major U.S. cities, one in five gay men is HIV-positive. Of 8,153 gay and bisexual men tested in the cities, 1,562 were positive. In Baltimore, 38 percent were positive; 29 percent in New York City; 26 percent each in Dallas and Houston; 23 percent in both Miami and San Francisco; and 21 percent in New Orleans.

- Nearly half of all infected gay/bi men don’t know they are HIV-positive. More than two-thirds of infected black men, and nearly eighty percent of HIV-positive young men aged eighteen to 24, are unaware they have the virus.

- As of 2008, AIDS had killed an estimated 617,025 Americans—48 percent (296,222) of them gay and bisexual men, most in the prime of life.

The CDC reported a strong link between men’s socioeconomic status and HIV. The lower a man’s income, the higher his risk for HIV. The higher his education and income, the more likely he was to know
his HIV status. There was no surprise in this confirmation that low income correlates to lack of insurance and late diagnosis of HIV-positive status.

**What Is To Be Done?**

So, what does HIV as a "gay" disease in America look like today? It looks a lot like other chronic, potentially fatal illnesses affecting people who need specialized medical care and costly treatments to keep them well. As with type 2 diabetes, high blood pressure, or treatable cancer, access to medical care and treatment is the key difference between living well with HIV or dying from AIDS.

The Obama administration’s signature health-care reform, the Affordable Care Act (ACA), which was upheld by the Supreme Court on June 28, 2012, has tremendous implications for people living with hiv/aids, particularly the law’s requirement (starting in 2014) that insurance companies can no longer deny coverage to the estimated 112 million Americans who have a pre-existing condition, including the estimated 1.1 million who are living with HIV. Since the court’s 5-4 ruling to uphold the law, the advocates are breathing a bit easier. However, according to Ronald Johnson, vice president for policy and advocacy with AIDS United, “it will be a brief sigh of relief. Now that we have the base of the ACA, and health care reform is in place, we have a huge agenda to make it work.”

Carl Schmid, deputy director of the AIDS Institute, observed that HIV advocates are now concerned about the implementation of the ACA, the expansion of Medicaid, and the need for the federal government to provide tools to the states and to service providers that rely on federal Ryan White Program funding. Schmid is concerned about what a Mitt Romney presidency would mean for the progress that has been achieved under President Obama. “The choices are really clear,” he said. “The Republicans are on record that they want to repeal this [ACA], and Romney as well. The Democrats and Obama are very clear they want to maintain the reform.”

As for hiv/aids and the GLBT equality movement, Schmid argued that the lack of visible involvement from the HRC and the Task Force has consequences beyond merely fueling the perception that hiv/aids isn’t a priority for them. It contributes to the dearth of public awareness about how hard-hit the gay male community continues to be.

Increasing that awareness, publicizing the fact that gay and bisexual men of all colors continue to bear the disproportionate burden of hiv/aids in the U.S., isn’t going to come about through three workshops at the Task Force’s “Creating Change” conference. It’s not likely that HRC’s issue brief will reach many members of the gay public, let alone the general public. What’s needed is for every GLBT organization in America to reclaim hiv/aids as a distinctly “gay” problem, one that affects the lives of hundreds of thousands of gay and bisexual men nationwide.

AIDS United’s Ronald Johnson sees responsibility for this project on both sides—the full-time HIV advocates and the national GLBT organizations: “Those of us in the HIV community, particularly those of us who straddle the communities, need to push and engage our brothers and sisters who are in the GLBT movement to get re-engaged. Those of us, gay men and lesbians of color, need to take on this challenge because gay and bisexual men continue to be the most impacted community in the United States. HIV is still a critical public health and individual health issue for the GLBT community.”

**Protein Critical to Gut Lining Repair Identified**

Scientists have identified a protein that is critical
ScienceDaily (Sep. 6, 2012) — Scientists at Washington University School of Medicine in St. Louis have identified a protein essential to repairing the intestine’s inner lining.

That lining is among the body's busiest highways, trod not only by the food we ingest but also by trillions of microorganisms that aid digestion. Because the intestine plays key roles in absorbing nutrients and containing the microbes, any damage must be fixed promptly.

that a protein called Wnt5a is essential for reconstructing glands in the intestinal lining. The glands, called crypts of Lieberkühn, contain stem cells that continually pump out other cells that renew the gut lining, which is replaced every two to four weeks. The crypts look like dimples in the gut lining and are vulnerable to damage and loss from infection and inflammation.

"For example, inflammatory bowel disease can destroy huge stretches of the lining, including the crypts," says senior author Thaddeus Stappenbeck, MD, PhD, associate professor of pathology and immunology. "If crypts can't be repaired as the lining is rebuilt, their absence would place substantial stresses on crypts in healthy portions of the gut. So it's important to better understand how the crypts are replaced."

In the new study, Stappenbeck and his colleagues showed that when crypts are lost to injury in mice, the nearest surviving crypts expand into the damaged area and create an array of channels. These wound channels, which contain rapidly dividing stem cells, eventually subdivide into new crypts.

Stappenbeck found that cells that line the outer wall of the gut migrate to sites of damage within the inner lining to provide Wnt5a, a signaling molecule that stops stem cells from dividing. This shutdown triggers the formation of dimples in the wound channels that become new crypts.

Because mice that lack the Wnt5a gene aren't viable, co-author Terry Yamaguchi, PhD, of the National Cancer Institute, bred mice in which scientists could selectively turn off the gene after the mice became adults. When the gut lining was injured and Wnt5a was disabled, the wound channels formed but failed to divide into crypts.

To further confirm the link between the gene and crypt repair, Hiroyuki Miyoshi, PhD, a postdoctoral fellow in Stappenbeck's laboratory, devised a robust method for growing gut stem cells in test tubes. When he applied Wnt5a to the stem cells, they stopped dividing, proving that the protein was the critical ingredient for initiating crypt formation.

The scientists also showed that Wnt5a activated a signaling pathway in the stem cells that is known to stop cell proliferation. Stappenbeck, who also is an associate professor of developmental biology, is now planning additional studies of Wnt5a, including investigations of whether the protein plays similar roles elsewhere in the body.

"We're also very curious about what causes the outer lining of the gut to send cells that make Wnt5a into the inner lining of the gut, because that's not something we've seen previously," he says. "Our best theory so far is that when this happens, the body may be reactivating a pathway it uses to construct the gut early in development."

Other researchers have identified the Wnt5a protein in tumors, suggesting it may play a role in cancer. Scientists don't know what that role is, but the new mouse model Yamaguchi developed may help solve the mystery.

Journal Reference:
Hiroyuki Miyoshi, Rieko Ajima, Christine T. Luo, Terry P. Yamaguchi, and Thaddeus S. Stappenbeck. Wnt5a Potentiates TGF-β Signaling to Promote Colonic Crypt Regeneration After Tissue Injury. Science, 6 September 2012 DOI: 10.1126/science.1223821

High rate of infections in people with HIV receiving Bio-Alcamid treatment for facial lipoatrophy
Michael Carter
Published: 10 September 2012

Bio-Alcamid treatment for HIV-related lipoatrophy is associated with a high-rate of infectious complications, Canadian investigators report in the online edition of Clinical Infectious Diseases. The infections typically developed years after initial therapy with Bio-Alcamid and dental work and facial manipulation were risk factors.

"We found an unacceptably high rate of infectious complications with the use of Bio-Alcamid," comment the investigators. "It is important that physicians recognize the high rate of infectious
complications associated with this product such that risks and benefits can be discussed with patients prior to this procedure.”

Facial lipoatrophy was recognised as a potential side-effect of antiretroviral therapy in 1998 and appears to be caused by older drugs in the NRTI class, most especially d4T (stavudine, Zerit). The only viable treatment for this often distressing and stigmatising side-effect is cosmetic surgery using injectable synthetic fillers.

Bio-Alcamid (polyalkylimide) is a non-reabsorbable polymer derived from acrylic acid. It has been extensively used for the treatment of antiretroviral-associated facial lipoatrophy in Europe and was licenced for this use in Canada in 2002.

Short-term clinical trials showed the safety and efficacy of the treatment. Despite this, doctors in Toronto noticed that a number of people were presenting with infections years after receiving Bio-Alcamid implants. They therefore conducted a retrospective study to determine the incidence and risk factors for infectious complications associated with Bio-Alcamid when used as a treatment for antiretroviral-associated facial fat loss.

A total of 267 people who received treatment between 2004 and 2010 were included in the analysis. Some 56 patients (19%) developed infections. The patients had a median age of 53 years, 96% were men and the median duration of infection with HIV was 16 years. All were taking HIV therapy, 92% had an undetectable viral load and median CD4 cell count was 500 cells/mm$^3$.

The overall incidence of infections was 0.10 per patient year. Infections occurred a median of 32 months after first treatment with Bio-Alcamid. A higher proportion of patients treated in 2004-05 developed an infection compared to those treated in 2006 or later (31 vs 8%, p < 0.0007). There was a 25% probability of developing an infection within 38 months of therapy.

“These figures are likely underestimates since patients with infections are more likely to present to the emergency room or their primary care physician,” write the investigators. “Patients or treating physicians may have been unaware of the potential link of infection to the filler.”

Dental work was reported by 31% of patients with infections and 8% said they had had cosmetic surgery. Touch-up treatment more than doubled the risk of infections (OR = 2.65; 95% CI, 1.12-6.16; p = 0.03).

“The risk of infection may be increased...for those requiring additional manipulation within the vicinity of the filler,” comment the authors, who suggest that prophylactic antibiotic therapy should be given to patients undergoing dental work or any other form of facial manipulation.

“Bio-Alcamid treatment for HIV-related facial lipoatrophy was associated with a high rate of infectious complications, often presenting years after treatment,” conclude the authors. “Patients should be counselled regarding the risks and long-term adverse effects of Bio-Alcamid.”

Reference

Analysis: Use of pill to prevent HIV may be limited in U.S
By Deena Beasley
LOS ANGELES | Fri Sep 7, 2012 1:17pm EDT
(Reuters)—The first preventive pill for HIV has been hailed as a landmark in the fight against AIDS in the United States, but experts say only a small percentage of those at risk will benefit from it.

U.S. health regulators last month approved Gilead Sciences Inc's Truvada —already used globally to treat the human immunodeficiency virus—for preventing the infection in healthy people at high risk of contracting the virus that causes AIDS.

A number of factors will limit the drug's use for preventing HIV, including the fact that in the United States many people most at risk of infection, as well as their sexual partners, do not have consistent access to healthcare. Even for those with coverage, insurance reimbursement for a $14,000-a-year drug is expected to be tricky.

In addition, therapy with the drug would require otherwise healthy young people to take a pill each day, plus show up for HIV testing every three months.

"There are a number of rather significant implementation challenges," said Dr. Stephen Morin, director of the Center for AIDS Prevention Studies at the University of California at San Francisco. "Part of it has to do with the requirement to take a pill a day, which could be addressed by a more long-term administration of the drug."
Scientists are exploring a variety of tactics for using AIDS drug formulations to prevent HIV infection, including long-acting injections, gels and vaginal rings. About 50,000 new HIV infections are reported each year in the United States. The number of patients taking Truvada to prevent HIV will likely be "a lot less" than that, said Howard Jaffe, head of the Gilead Foundation and a member of the company's senior management since 1991.

Gilead declined to give its own sales estimate. "We are not expecting a meaningful increase or uptick in Truvada use from it," Jaffe said, referring to the FDA prevention approval. "We do expect it to enter into the conversation with regard to certain high-risk populations."

He said use of Truvada to prevent HIV infection will likely be most important outside of the United States, as developing countries where AIDS remains an epidemic look for additional ways to curb transmission of the virus.

Gilead has deals, mainly with generic drugmakers in India, to produce low-cost versions of its drugs for use in sub-Saharan Africa and other developing regions.

Dr. Paul Volberding, director of the Center for AIDS Research at the University of California at San Francisco, says Truvada could become a valuable tool for "a small fraction of people" who understand they have a high risk of exposure—mainly female sex workers whose clients won't use condoms and gay men who decide they are going to engage in riskier sex.

"There is an easy consensus now that somebody that is on treatment and fully suppressed has either zero, or close to it, risk of transmitting the virus," Volberding said.

He and others emphasized that wider testing for HIV—and treatment of already infected patients—are the keys to reducing HIV incidence.

Of the 1.2 million Americans estimated to be infected with human immunodeficiency virus, almost 20 percent of them do not know it, according to the U.S. Centers for Disease Control and Prevention.

A recent study by the CDC found that 41 percent of U.S. HIV patients are under continual care of a doctor and just 28 percent had the viral infection under control.

Prevention Through Prep
The U.S. Food and Drug Administration in July approved Truvada for adults who do not have the virus but may engage in sexual activity with HIV-infected partners, a concept known as pre-exposure prophylaxis (PrEP). The approval was for use in combination with safer sex practices, such as condoms.

The drug, which combines two anti-HIV drugs in one pill, was already approved for use with other antiretroviral agents to treat patients 12 and older who are infected with the virus. Antiretrovirals are designed to block various steps in replication of the virus.

Critics, including the AIDS Healthcare Foundation, a non-profit provider of HIV/AIDS medical care, argue that Truvada was shown to be only partially effective in preventing HIV transmission, can cause side effects including kidney problems and may cause healthy people to become resistant to it.

No U.S. public money has been allocated for treating uninsured individuals who do not already have AIDS, and some doctors question the degree to which insured patients would be covered.

"I would find it very difficult for there to be a provision to support funding for such a program when we have (HIV-positive) patients on waiting lists," said Murray Penner, deputy executive director at the National Alliance of State and Territorial AIDS Directors, which represents public-health departments.

State AIDS Drug Assistance Programs (ADAPs), which provide HIV treatment to low-income and uninsured patients, had 9,000 people on waiting lists a year ago. That number fell to 700 in mid-August after emergency federal funding was released, although many recession-battered states have tightened income criteria, reducing the number of eligible patients.

ADAPs generally have a total of more than 200,000 people enrolled in them over the course of a year, Penner said.

A Rounding Error In Sales Terms
Gilead, like other drugmakers, sells its HIV pills to ADAP programs at a significant discount. "When we talk to our physician consultants who target HIV patients, they say they are not going to use much of it (Truvada) for prevention," said Phil Nadeau, an analyst at Wall Street firm Cowen & Co.

Any use of Truvada for preventing HIV infection "seems to be a rounding error in our estimates for treating HIV," he said, projecting Gilead's 2012 sales from the drug at $3.1 billion.

RBC Capital Markets described the prevention indication as a "niche" opportunity for Gilead, while Morgan Stanley said it "looks like a modest opportunity but many questions remain."

The CDC has recommended since early 2011 that high-risk gay and bisexual men should use the drug to protect against HIV.
Large insurers such as UnitedHealth Group Inc, WellPoint Inc and Aetna Inc say they cover Truvada for prevention as well as treatment of HIV, but are still deciding whether to institute rules about authorization.

Doctors remain skeptical that insurers will pay for Truvada without complicated documentation showing why a patient is high-risk and whether PrEP is the best preventive measure.

"It's not quite clear to me whether or not I'm going to be prescribing it," said Dr. Mehri McKellar, an infectious disease expert at Duke University in North Carolina. She described one HIV-positive patient whose male partner had not been infected.

"They had read about PrEP, but they use condoms 100 percent of the time," she said. "This is not supposed to at all replace condom use. It's not clear whether we should be talking about PrEP."

(Additional reporting by Julie Steenhuysen; Editing by Michele Gershberg and Douglas Royalty)

### Related Quotes and News

<table>
<thead>
<tr>
<th>Company</th>
<th>Aetna Inc (AET.N)</th>
<th>Gilead Sciences Inc (GILD.O)</th>
<th>UnitedHealth Group Inc (UNH.N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Price</td>
<td>$38.20</td>
<td>$59.66</td>
<td>$53.74</td>
</tr>
<tr>
<td>Related News</td>
<td>-0.80-2.05%</td>
<td>+0.40-0.67%</td>
<td>-1.14-2.08%</td>
</tr>
</tbody>
</table>

**Maryland man faces rarely used HIV transmission charges**

**By Jessica Anderson | The Baltimore Sun, Monday, September 10, 11:32 AM**

When police accused an Edgemere man of having sex with a 13-year-old boy, most of the charges were straightforward: soliciting a minor and a related sexual offense, which together could carry up to 30 years in prison.

But Baltimore County prosecutors also accused Steven D. Podles of knowingly attempting to transmit the HIV virus to the boy — a seldom-used and often controversial charge that carries an additional three years behind bars.

Even as prosecutors prepare their case against Podles, the effectiveness of such laws is being debated by legislators and public health officials from Maryland to California.

During the height of the AIDS scare in the 1980s and 1990s, 33 states — including Maryland — passed laws to criminalize the spread of HIV. And in cases around the nation, some defendants have been hit with attempted murder charges and decades-long sentences.

Now, though, public health advocates say such charges are arcane and ineffective, discouraging people from getting tested and perpetuating stigmas against those with the disease. In recent years, the federal government has modified its HIV/AIDS policy, recommending against HIV criminalization.

“One has to ask if [prosecuting such cases] has any value to public health,” said Scott Burris, a Temple University law professor whose research contributed to new national strategies against the spread of HIV.

“This doesn’t make any difference to HIV prevention.”

Although a growing number of critics are arguing against HIV-related charges, many law enforcement officials maintain that such criminal penalties are necessary. Some states have strict laws that equate passing on the virus with using a deadly weapon.

“I don’t know that any prosecutors are opposed to the notion [of filing charges] if anyone passes the HIV virus to another and there’s no disclosure. It’s unconscionable,” said Scott Burns, executive director of the National District Attorneys Association.

The charge, however, is seldom used in Maryland and it can be difficult to get a conviction.

Baltimore County State’s Attorney Scott D. Shellenberger said he is unaware of any similar cases in the county.

Shellenberger said the charge is not easy to prove. “We have to prove [that a defendant] knowingly transferred” or attempted to transfer the virus,” he said. “Being able to meet all of these elements, it’s a little more challenging.”

Still, in the Essex case, prosecutors believe they have enough evidence for a conviction, he said.

Isaac Klein, Podles's attorney, called the charge “outrageous. I guess one way is to overcharge, for my client to plea to something.”

When Podles contacted the teen in February, Klein said, his client’s intention was to meet with other adults using the mobile phone application, Grindr, which is supposed to be limited to those who are 18 and over.

He added, “even if both of them have [HIV], you can’t prove it was from my client.”
The criminalization laws, designed to prevent those who are HIV-positive from intentionally spreading the disease and putting others in harm, have been used in high-profile prosecutions across the country. Defendants have been convicted for knowingly spreading the virus, or attempting to do so, through sexual contact or by sharing syringes.

In 1987, an Indiana man was arrested on attempted murder charges after spitting blood at officers; he died in prison of complications related to AIDS while serving a 30-year sentence. In 2008, a Texas man who was HIV-positive was sentenced to 35 years in prison for spitting on a police officer.

That same year, an Iowa man was sentenced to 25 years in prison after a former partner went to police because of his exposure to the virus. The man who was charged told CNN that his viral load was lower from treatment, making the disease almost non-detectable, and that he used a condom, which reduces the risk.

Critics say such prosecutions make people fearful of getting tested and being held liable for knowingly spreading the disease. Those who know they carry the virus are more likely to take precautions to prevent its spread, they say.

“The HIV-specific statutes aren’t necessary and serve only to stigmatize and make the epidemic worse,” said Sean Strub, who is founder of the SERO Project, a nonprofit that advocates for those with HIV, and U.S. co-chair for the Global Network of People Living with HIV. “Every state has assault statutes and public health statutes that provide for appropriate charges or measures if someone intends to or does harm someone, or poses an imminent risk of danger to himself or herself or others.”

He likened HIV-specific statutes to those that would single out individuals based on gender, sexual orientation, genetic makeup or skin color. “It is inherently discriminatory to create different laws for different groups of people,” he said.

Burris and Strub point to cases where heavier sentences were imposed on individuals with the virus — which, they argue, heightens fear and discourages others from getting tested. In one common scenario, they said, a couple breaks up, and one partner threatens to file charges against the other who is HIV-positive.

In a July study conducted by the SERO Project, 2,000 people living with HIV were interviewed, and nearly half said it was reasonable to put off testing to avoid potential prosecution. The study also found that a quarter of those interviewed knew others who were reluctant to get tested for the virus due to the same concerns.

Although law enforcement officials around the country continue to bring charges related to HIV transmission, the federal government has recommended shifting away from such policies.

Two years ago, President Obama announced a new National HIV/AIDS Strategy that recommended against HIV criminalization.

“While we understand the intent behind such laws, they may not have the desired effect and they may make people less willing to disclose their status by making people feel at even greater risk of discrimination,” the report said.

The report also noted advances in medical treatment. “HIV medications can extend the length and quality of life for infected individuals, and lower the amount of the virus circulating in a person’s body, thereby reducing their risk of transmitting HIV to others,” the report said.

The Centers For Disease Control and Prevention, meanwhile, advises that “State legislatures should consider reviewing HIV-specific criminal statutes to ensure that they are consistent with current knowledge of HIV transmission and support public health approaches to preventing and treating HIV.”

Last year, California Rep. Barbara Lee (D) proposed the first piece of legislation to require states to repeal such laws; it did not pass.

But as the federal government has suggested re-evaluating such laws, bills were proposed in the last Maryland General Assembly session to toughen state laws, making HIV transmission a felony instead of a misdemeanor, and calling for a 25-year sentence.

Sen. Norman R. Stone Jr., a Baltimore County Democrat, and Del. C.T. Wilson, a Charles County Democrat, were the bills’ lead sponsors. Neither Stone nor Wilson returned calls for comment.

The ACLU of Maryland testified against the proposal. In a statement, the ACLU wrote, “Increasing the HIV-specific disclosure law in Maryland to a felony is wildly out of proportion to the possible harm, and is in bizarre and direct conflict with the direction of public health, human rights and the substantially decreased consequences of HIV disease in the last 15 years.”

Instead of sentencing to prison those who might spread the virus, policies should focus on encouraging the public to protect themselves and get tested, Burris said. “Punishing people who don’t tell doesn’t make sense.”
RV144 vaccine efficacy increased against certain HIV viruses
Findings reinforce specific target on the virus for vaccines
September 10, 2012 (SILVER SPRING, Md.) – Scientists used genetic sequencing to discover new evidence that the first vaccine shown to prevent HIV infection in people also affected the viruses in those who did become infected. Viruses with two genetic "footprints" were associated with greater vaccine efficacy. The results were published today in the online edition of the journal *Nature*.

"This is the first time that we have seen pressure on the virus at the genetic level due to an effective HIV vaccine," said Morgane Rolland, Ph.D., a scientist at the U.S. Military HIV Research Program and lead author of the study. The analysis revealed evidence of a vaccine-induced immune response on two sites of Env-V2 region located on HIV's outer coat. For viruses carrying these two particular signatures, the vaccine efficacy increased to 80 percent.

"These findings reinforce both the RV144 result and the previous study showing that antibodies directed at the V1V2 region reduce the risk of infection. Taken together the work suggests that the Env-V2 region could be a critical target for future HIV vaccines," noted Col. Jerome Kim, senior author on the study.

"Genetic sequencing is an important and independent assessment of the immune responses induced by the vaccine," said Paul Edlefsen, Ph.D., a biostatistician at the Statistical Center for HIV/AIDS Research and Prevention (SCHARP) who co-led the study. Researchers examined HIV genome sequences from 110 volunteers who participated in the Thai HIV vaccine trial, RV144, and who subsequently became infected with HIV. Results indicate that the HIV viruses infecting trial participants were different in persons who received vaccine compared to those who received placebo.

Researchers focused their analysis on the V2 portion of the HIV virus after a study published earlier in 2012 found that antibodies specific to the V1V2 region of the HIV genome correlated with lower risk of infection. This new genetic sequencing study showed that the viruses that broke through or escaped from these immune responses have genetic differences in the same V2 region, indicating that the vaccine exerted pressure in this region.

HIV viruses that escape from antibodies and manage to infect a person have genetic footprints, or mutations, that can prevent them from being recognized by the immune system. These changes can be seen in the genetic sequence of the virus. The research team sequenced more than a thousand full-length viruses to look very carefully at which changes corresponded to "escape" mutations.

"This study underscores the realistic optimism you see in the HIV vaccine research field today. We are making substantive progress in understanding what it will take to develop a more effective HIV vaccine which will ultimately help us end this pandemic." said Col. Nelson Michael, director of MHRP.

The study team included researchers with the U.S. Army's Military HIV Research Program (MHRP) at the Walter Reed Army Institute of Research, The Statistical Center for HIV/AIDS Research and Prevention (SCHARP) at the Fred Hutchinson Cancer Research Center and the University of Washington. The project was supported by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, and a cooperative agreement between the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., and the U.S. Department of Defense (DoD).

**References:**
3. For additional information and photos, please visit [www.hivresearch.org](http://www.hivresearch.org)

**About RV144**
Results from RV144, an Army-led clinical trial involving more than 16,000 adult volunteers in Thailand, were published in the New England Journal of Medicine in 2009. The results showed that the prime-boost combination of ALVAC® HIV and AIDSVAX® B/E was safe and lowered the rate of HIV infection by an estimated 31.2% compared with placebo (p=0.04). These data provided the first evidence in humans that a safe and effective preventive HIV vaccine is possible.

Results from extensive RV144 laboratory studies were published On April 5, 2012 in the New England Journal of Medicine. These studies showed that antibodies (IgG) specific to a particular region (called V1V2) of the HIV outer coat (envelope protein) correlated with lower infection rates among those who were vaccinated.
AIDS Spreading Fast Across East Europe

*Inter Press Service*, (09.03.2012) Pavol Stracansky

Eastern Europe and Central Asia are home to the world’s fastest-growing HIV epidemic, due to punitive drug policies, discrimination, and insufficient access to medicines and treatment, according to global health experts.

World Health Organization data show the region had 170,000 new HIV infections last year. New infections there have risen 22 percent since 2005 and show no signs of slowing. Injecting drug use accounts for 70 percent of new cases.

Russia and Ukraine are widely viewed as the epidemic’s epicenter. Opiate-substitution therapy (OST), a standard treatment provided to heroin users in much of the world, is illegal in Russia.

Although OST and needle-exchange programs have ostensible government support in the Ukraine, “Physical and other intimidation towards drug users is routine police practice,” said an in-country spokesperson for the International HIV/AIDS Alliance. Further, the group reports that the denial of antiretroviral treatment to infected drug users is a “common problem.”

“In most post-Soviet countries, where HIV remains concentrated among injecting drug users, harsh policies and discrimination in health care settings continue to cripple the AIDS response,” noted Daniel Wolfe, director of the International Harm Reduction Development Program at the Open Society Foundations.

Most Asian Countries Fail To Include Rotavirus Vaccine In National Immunization Programs Citing Cost As Barrier

"Most countries in Asia have yet to make the rotavirus vaccine part of their national immunization program (NIP), despite a World Health Organization (WHO) recommendation to do so," IRIN reports. "Worldwide, rotavirus accounts for 37 percent of all diarrhea deaths in children under five with 95 percent of those deaths occurring in developing countries," the news service states, noting, "There are no antibiotics or any other drug to fight the infection and since 2009 WHO has recommended the global use of the rotavirus vaccine." Forty-one countries worldwide include rotavirus vaccine in their NIPs, but "only two countries in Asia—Philippines and Thailand—are vaccinating (or are about to) children against rotavirus," according to IRIN. An email to IRIN from WHO’s Manila office stated, "Price continues to be an important barrier to introducing rotavirus vaccine," the news service notes (9/7).

Success And Failure In Fighting Cholera In Haiti

"Almost two years after the deadly disease first appeared in Haiti in the aftermath of the Jan. 12, 2010 earthquake, the story of cholera is one of both success and failure,” columnist Catherine Porter writes in a Toronto Star opinion piece. She says though progress has been made in bringing down the death rate from cholera, educating the population on prevention, and getting people with the disease into treatment more quickly, aid agencies’ funding has "dried up and most have ended their cholera programs." She continues, "In most instances, the Haitian government has not picked up the work that had been done by departing aid agencies. ... For its part, the Haitian government has focused on surveillance and prevention—plastering the city with posters about hand-washing and disinfecting water."

"One year before cholera appeared in Haiti, there were around 221,000 reported cases and 4,950 deaths to cholera globally, according to the World Health Organization. In less than two years, little Haiti has seen more than 586,000 cases and 7,500 deaths to cholera," Porter notes. She describes efforts to vaccinate a small percentage of the population and the construction of state-of-the-art waste water treatment plants. "On the second anniversary of the earthquake, the World Health Organization launched a campaign to eliminate cholera from both Haiti and neighboring Dominican Republic over the next decade," she states, continuing, "WHO Regional Deputy Director Jon Andrus puts the cost at $2.4 billion—less than half the amount pledged to Haiti in aid money after the earthquake, most of which is still undelivered, he points out" (9/8).

Middle-aged people with HIV have a high risk of falls

Michael Carter
Published: 11 September 2012

Falls are common among middle-aged people with HIV, US investigators report in the online edition of the *Journal of Acquired Immune Deficiency Syndromes*. Over twelve months, almost a third of people in the study (30%) experienced a fall.
“We found that the fall rate in middle-aged adults...with HIV-1 infection, is as common as in uninfected persons aged 65 years or older,” comment the authors. “Falls in our cohort were associated with several previously reported risk factors such as hypertension, diabetes, impaired balance, and pain, as well as medications used in the treatment of these comorbidities.”

Falls are common among older adults, occurring in a third of over-65s each year. They are a frequent cause of emergency hospital admission and can result in loss of independence.

HIV infection appears to be a risk factor for a number of diseases of ageing. Moreover, there is also a high prevalence of traditional risk factors for falls such as diabetes, pain, depression, neuropathy and use of psychoactive medications among people living with HIV.

“We hypothesized that a greater number of fall risk factors would result in a higher than expected fall rate among middle-aged HIV-1-infected adults,” write the investigators.

They therefore designed a study involving 359 people who received care in Colorado between early 2009 and early 2010. All were aged between 45 and 65 and were taking antiretroviral therapy with an undetectable or low viral load (at least one undetectable measurement and no measurement above 200 copies/ml).

Most of the study participants (85%) were men, 74% were white, 65% were gay men and 21% had a history of injecting drug use. The mean age was 52 years, mean CD4 cell count was 594 cells/mm³ and 95% had an undetectable viral load.

A total of 109 people (30%) reported at least one fall in the previous year. Almost two-thirds (61%) of those experiencing a fall had multiple falls. Women and smokers were more likely to have recurrent falls (p < 0.05).

The investigators believe these figures underestimate the incidence of falls in people with HIV who are doing less well on antiretroviral therapy, as well as those “with advanced immunodeficiency, or with greater intravenous drug abuse.”

No HIV-related factor was associated with an increased risk of fall. Analysis failed to find any association with either nadir and current CD4 cell count or viral load. There was a weak association with longer duration of HIV infection, but this failed to reach significance.

However, the presence of other health problems did increase the risk of falls. Each additional co-morbidity increased the risk of falling by 70% (OR = 1.7; 95% CI, 1.5-2.1, p < 0.001).

Use of medication was also associated with the risk of falling. Each additional medication increased the risk of falls by 40% (OR = 1.4; 95% CI, 1.3-1.6, p < 0.001). Medications associated with a risk of falling included beta-blockers, antidepressants, sedatives and opiates (p < 0.01). The investigators also found evidence of an association with falls and the older anti-HIV drugs d4T (stavudine, Zerit) and ddI (didanosine, Videx). A recognised side-effect of these drugs is neuropathy, a known risk factor for falls.

Frailty and disability were also associated with an increased risk of falls (p < 0.001). In addition, people who had recurrent falls had a significantly slower walking pace compared to people who didn’t fall (p < 0.001).

After controlling for potential confounders, the researchers found that a number of factors were associated with falls. These included female gender, diabetes, antidepressants, treatment with sedatives, opiates, HIV therapy that included ddI, exhaustion, weight loss and difficulty with balance. All more than doubled the risk of falls (p ≤ 0.05).

“Ultimately, the best predictors of fall risk were those factors known to be associated with fall risk in geriatric populations,” write the investigators.

“Given that multiple factors lead to increased fall risk, it is expected that successful interventions to reduce falls in HIV-infected persons will require a multipronged approach including medication adjustment, behavioural modifications, vitamin D supplementation, physical therapy, and exercise or balance programmes,” the authors suggest.

They recommend “providers caring for HIV-infected persons should routinely inquire about falls, assess fall risk factors for those at risk for falling, and when high risk is identified, intervene to reduce risk.”

Reference
Double trouble: daily function and the impact of old age and HIV
Michael Carter
Published: 11 September 2012

Older age exacerbates the deleterious effect of HIV on daily functioning, investigators from the US report in the online edition of the Journal of Acquired Immune Deficiency Syndromes. Investigators compared ability to perform daily tasks, cognitive function and quality of life between patients according to their age and HIV infection status.

“For each of the functional outcomes, the older HIV+ group demonstrated poorer everyday functioning relative to other study groups,” comment the authors. “These findings suggest that older age may exacerbate HIV-associated disability in daily life.”

The investigators believe their findings have important implications for HIV care, which should focus on the early detection of functional problems and their causes.

Thanks in part to the success of antiretroviral therapy, the population living with HIV in the US and other industrialised countries is ageing. Data from the US Centers for Disease Control (CDC) suggest that a quarter of all people with HIV are now aged over 50. As they age, they become more vulnerable to age-related disorders such as cardiovascular disease, changes in bone mineral density and neurocognitive impairment.

Investigators hypothesised that HIV infection would exacerbate the declines in daily function that are associated with these diseases of old age and ageing generally. They therefore designed a cross-sectional study involving 103 people living with HIV and 87 HIV-negative controls. They examined the factors associated with everyday functioning and quality of life between those aged under 40 and those aged over 50.

A wide spectrum of tests was used to assess functioning. These included:

- Instrumental activities of daily living (IADL): financial management, purchase of groceries, cooking, using transport, shopping, managing medication and planning social activities.
- Basic activities of daily living (BADL): cleaning, laundry, home repairs, dressing and bathing.
- Karnofsky score on a range of 100 (able to carry out normal activities) to zero (death).
- Questionnaires assessing both physical and mental health-related quality of life.
- Medical evaluation: assessment of co-morbidities common in older people living with HIV, including diabetes, cardiovascular disease, respiratory disease and hepatitis C co-infection.
- Neuropsychiatric assessment: monitoring for HIV-related neurocognitive impairment.
- Psychiatric evaluation: assessment of current mood and history of major depression and substance abuse.

The older group of people with HIV had an average age of 55 years and 71% were male. They had been living with HIV for a median of 18 years. Their median nadir CD4 cell count was 148 cells/mm³. All were taking antiretroviral therapy and 90% had an undetectable viral load. This group had a high prevalence of co-morbid conditions. A quarter had a current major depression and half had a lifetime history of depression. Over a third were co-infected with hepatitis C, 10% had cardiovascular disease, 15% had been diagnosed with diabetes and 5% had a respiratory complaint.

There was a significant interaction between ageing and HIV regarding IADL scores (p = 0.025), BADL scores (p = 0.043) and Karnofsky score (p = 0.001).

Factors associated with lower IADL scores for older people with HIV included cognitive impairment (p = 0.043), current major depression (p = 0.002), nadir CD4 cell count (p = 0.023) and lack of “cognitive reserve” – engagement with intellectual and social activities (p = 0.028).

BADL severity was associated with current depression (p = 0.007). A lower Karnofsky score for elderly people with HIV was also related to current depression (p = 0.016), as were having other serious health problems (p = 0.008) and lack of cognitive reserve (p = 0.016).

Poorer self-rated mental health-related quality of life in older people with HIV was also attributed to the additive effects of age and HIV.

“Several of these predicators are highly amenable to proper screening and treatment,” note the researchers. “For example, major depression was arguably the most reliable predictor of adverse functional outcomes in our older HIV+ cohort...these findings highlight the need to regularly screen older HIV+ adults for symptoms of depression given that major depression can disrupt performance of important daily activities and are potentially remediable.” They note that the best outcomes are seen in people who are treated with both antidepressants and psychotherapy.
The investigators also highlight the association between cognitive reserve and daily function. “This evidence suggests that in older HIV-infected adults, lower cognitive reserve may interfere with the adaptive ability to engage alternate brain networks and/or initiate alternate brain networks and/or initiate use of compensatory strategies when they encounter problems in their daily life, resulting in disability.”

Reference

AIDS Vaccine Sleuths Find New Clues as 30-Year Hunt Continues
By Simeon Bennett – Sep 10, 2012 8:30 AM ET

AIDS researchers found clues that help explain why an HIV vaccine worked better for some people than others in a study, advancing scientists’ understanding of the virus.

Researchers identified two genetic “signatures” in the virus among people who contracted HIV despite being vaccinated in a 2009 trial in Thailand. Those genetic features may have helped the virus to evade the vaccine, according to the U.S. Military HIV Research Program in Silver Spring, Maryland, which published the findings today in the journal Nature. The study is also being presented at an AIDS conference in Boston.

July 25 (Bloomberg) — Timothy Ray Brown, the only person in the world believed to have been cured of HIV, talks about how his body has been cleared of the virus. Brown’s HIV was wiped out after getting a bone marrow transplant in 2007 for cancer. The donor had a rare gene mutation that made the new white blood cells resistant to infection with the AIDS virus. Brown spoke yesterday at a news conference in conjunction with the International AIDS Conference in Washington. (Source: Bloomberg)

The new research shows that the vaccine, the only one that has shown any success fighting HIV, was more effective combating the virus when the signatures included one specific mutation and lacked another one, protecting in as much as 80 percent of the cases. The findings may help scientists design future vaccines, said Jerome Kim, who led the research.

“It’s as though you had 50 different kinds of fish that can potentially be caught, and you catch most of them, but by looking at the ones that escaped you can tell what the problems are with the net,” Kim said in a phone interview.

The 2009 trial on Sanofi (SAN)’s Alvac and VaxGen Inc.’s Aidsvax surprised researchers by showing that the two vaccines, which had failed in tests on their own, reduced infections by 31 percent over three years when used in combination. Researchers have been scouring the blood of participants in the trial for clues to help improve on the result.

V2 Loop
Kim and colleagues found the two genetic features in an area of the virus’s outer coat called the V2 loop, an area on HIV’s surface that is constantly changing, confounding vaccine hunters for more than three decades.

An analysis published in April showed that those who were protected against HIV in the trial developed antibodies against the V2 loop, suggesting the region plays a key role in the virus’s ability to infect, Kim said.

Today’s findings combined with the April study show that the antibodies generated by the vaccine forced the virus to mutate to escape it, Kim said.

Kim and colleagues are part of a consortium called the Pox Protein Public-Private Partnership that is planning follow-on trials to the Thai study, including one in South Africa where it’s hoping to generate a larger and longer-lasting response to V2.

Oxyphenbutazone can kill drug resistant TB
Published on September 11, 2012 at 12:29 AM

Inflammatory drug that costs around two cents for a daily dose in developing countries has been found by researchers at Weill Cornell Medical College to kill both replicating and non-replicating drug resistant tuberculosis in the laboratory—a feat few currently approved TB drugs can do, and resistance to those is spreading.

Their findings, published online by the journal PNAS, point to a potential new therapy for the more than 500,000 people worldwide whose TB has become resistant to standard drug treatments. But the researchers worry that the effective drug, oxyphenbutazone, may never be tested in TB clinical trials.
Weill Cornell's Dr. Carl Nathan and his research team found what they call the "completely surprising" ability of oxyphenbutazone to kill drug resistant TB after testing thousands of approved drugs against the bacteria. This repurposing of agents already on the market can lead to quicker testing for new uses.

"This agent might help save lives if there was a way to test it in TB patients," says Dr. Nathan. Oxyphenbutazone went on the market as a patented drug for arthritis-like pain in the early 1950s, and lost its patent and market dominance by the 1970s.

"It is difficult today to launch clinical studies on a medication that is so outdated in the United States, that it is mainly used here in veterinary medicine to ease pain," says the study's senior author, Dr. Nathan, chairman of the Department of Microbiology and Immunology, the R.A. Rees Pritchett Professor of Microbiology, and the director of The Abby and Howard Milstein Program in the Chemical Biology of Infectious Disease at Weill Cornell. "No drug firm will pay for clinical trials if they don't expect to make a profit on the agent. And that would be the case for an off-patent drug that people can buy over the counter for pain in most of the world."

He adds that oxyphenbutazone, best known under the trademark name of Tandearil, does have some established toxicities, "and is not a drug you should take for aches and pains if a safer alternative is available." But the drug's major toxicities appear to be less frequent than the major side-effects of the drug regimens that are currently used to treat TB, he says.

**Treating the TB that Hides**

*Mycobacterium tuberculosis* is unusual among disease-causing bacteria in that it naturally infects just humans. One-third of the world’s population is infected with TB, but the bacteria typically remain dormant in a person with a healthy immune system.

Nonetheless, TB becomes active in enough people that it is the leading cause of death in humans from a bacterial infection. It is difficult to treat, and the bacteria can become resistant to therapy. TB treatment in a drug-sensitive patient takes six months, using a combination of agents. If the TB is sensitive to these first-line agents and the therapy is completed with full-strength, non-counterfeit drugs, up to 95 percent of patients can be cured.

However, if a patient’s TB becomes resistant to these drugs, second-line agents are administered every day for two years or more. "These second-line drugs are often toxic and expensive, and are not readily available in developing countries, where most of the infections occur," Dr. Nathan says. Mortality in drug resistant TB patients can be as high as 80 percent.

A major issue in treating TB is that the bacteria can "hide out" in the body in a non-replicating form, even when a TB patient is undergoing treatment.

To find agents that could attack non-replicating TB, Dr. Nathan’s research team first identified four conditions that keep bacteria in that state within the human body: low oxygen, mild acidity, a fat instead of sugar to eat and a small amount of the natural defense molecule nitric oxide.

The research team replicated those conditions in the test tube and then methodically tested the effectiveness of thousands of agents against the bacteria. After testing 5,600 drugs, researchers found oxyphenbutazone.

Researchers then delved into the mechanism by which oxyphenbutazone kills TB and found that the conditions that allow the bacterium to remain dormant modify the drug to the point that it starts reacting against both non-replicating and replicating TB. "When this happens, TB can’t defend itself and dies," Dr. Nathan says.

But the researchers were unable to test oxyphenbutazone in mice, because the animals metabolize the drug to an inactive form far faster than humans.

"This makes testing the drug for TB use in humans problematic since the FDA requires preclinical animal testing studies for safety and efficacy," Dr. Nathan says. "Yet there is a long track record of oxyphenbutazone’s relatively safe use in hundreds of thousands of people over decades."

Dr. Nathan and his team are continuing their research, testing hundreds of thousands of compounds for their action against TB. His team has already found another approved drug, nitazoxanide, to be effective against the bacteria, publishing his findings in 2009.

Nitazoxanide, a drug with an excellent safety record, is still on patent for use against some infections caused by other microbes. Discussions have been held about testing it in TB, Dr. Nathan says, but have stalled because of the same problem as oxyphenbutazone. The drug is metabolized so quickly in mice that it cannot be tested against experimental TB in that species.

For both oxyphenbutazone and nitazoxanide, Dr. Nathan argues that the requirement for testing in animals with experimental TB should be waived, because these agents work against TB in the test tube,
have already been used with relative safety in people and might address an urgent need for treatment of a contagious disease with high mortality and few other treatment options.

**UCLA stem cell researchers use gene therapy to restore immune systems in 'bubble babies'**

UCLA stem cell researchers have found that a gene therapy regimen can safely restore immune systems to children with so-called "Bubble Boy" disease, a life threatening condition that if left untreated can be fatal within one to two years.

In the 11-year study, researchers were able to test two therapy regimens for 10 children with ADA-deficient severe combined immunodeficiency (SCID). During the study, they refined their approach to include a light dose of chemotherapy to help remove many of the blood stem cells in the bone marrow that are not creating an enzyme called adenosine deaminase (ADA), which is critical for the production and survival of healthy white blood cells, said study senior Dr. Donald Kohn, a professor of pediatrics and of microbiology, immunology, and molecular genetics in Life Sciences and a member of the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA.

The refined gene therapy and chemotherapy regimen proved superior to the other method tested in the study, restoring immune function to three of the six children who received it, Kohn said. Going forward, an even further refined regimen using a different type of virus delivery system will be studied in the next phase of the study, which already has enrolled eight of the 10 patients needed.

The study appears Aug. 30 in the advance online issue of the peer-reviewed journal *Blood*.

"We were very happy that in the human trials we were able to see a benefit in the patients after we modified the protocol," Kohn said. "Doctors treating ADA-deficient SCID have had too few options for too long, and we hope this will provide them with an efficient and effective treatment for this devastating disease."

Children born with SCID, an inherited immunodeficiency, are generally diagnosed at about six months. They are extremely vulnerable to infectious diseases and don't grow well. Chronic diarrhea, ear infections, recurrent pneumonia and profuse oral candidiasis commonly occur in these children. SCID cases occur in about 1 of 100,000 births.

Currently, the only treatment for ADA-deficient SCID calls for injecting the patients twice a week with the necessary enzyme, Kohn said, a life-long process that is very expensive and often doesn't return the immune system to optimal levels. These patients also can undergo bone marrow transplants from matched siblings, but matches can be very rare.

About 15 percent of all SCID patients are ADA-deficient. Kohn and his team used a virus delivery system that he had developed in his lab in the 1990s to restore the gene that produces the missing enzyme necessary for a healthy immune system. To date, about 40 children with SCID have received gene therapy in clinical trials around the world, Kohn said.

Two slightly different viral vectors were tested in the study, each modified to deliver healthy ADA genes into the bone marrow cells of the patients so the needed enzyme could be produced and make up for the cells that don’t have the gene. Four of the 10 patients in the study remained on their enzyme replacement therapy during the gene therapy study. There were no side effects, but their immune systems were not sufficiently restored, Kohn said.

In the next six patients, the enzyme therapy was stopped and a small dose of chemotherapy was given before starting the gene therapy to deplete the ADA-deficient stem cells in their bone marrow. Of those patients, half had their immune systems restored. The human findings confirmed another study, also published recently in *Blood* by Kohn and UCLA colleague Dr. Denise Carbonaro-Sarracino, which tested the techniques in parallel, using a mouse model of ADA-deficient SCID.

One of Kohn's clinical trial patients enrolled in the first study was a baby boy diagnosed with ADA-deficient SCID at age 10 months. The boy had multiple infections, pneumonia, and persistent diarrhea and was not able to gain weight. He received the enzyme replacement treatment for three to four months, but did not improve and joined the gene therapy study in 2008. Today, that boy, who lives with his family in Arizona, is a thriving 5-year-old.

"You would never know he had been so sick," Kohn said. "It's a very promising response."

The boy's younger sister, also born with ADA-deficient SCID, was diagnosed at age four months and is enrolled in the second phase of the study. She's also doing well, Kohn said. In fact, it appears that children who are diagnosed and treated younger seem to do better.
Reconstructed 1918 influenza virus has yielded key insights, scientists say
The genetic sequencing and reconstruction of the 1918 influenza virus that killed 50 million people worldwide have advanced scientists’ understanding of influenza biology and yielded important information on how to prevent and control future pandemics, according to a new commentary by scientists at the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, and several other institutions.

By sequencing the 1918 virus, researchers were able to confirm that the viruses that caused influenza pandemics in 1957, 1968, and 2009 were all descended in part from the 1918 virus. Studies showed that the 2009 pandemic virus had structural similarities with the 1918 virus and explained why younger people, who had never been exposed to the 1918 virus or its early descendants, were most vulnerable to infection by the 2009 influenza virus. As a result, public health officials were able to target limited vaccine supplies to predominantly younger people, who needed vaccine protection most, rather than the elderly, who were at lower risk of infection in 2009, but are traditionally the most important target group for vaccination. Further, determining the physical structure of parts of the 1918 virus, particularly the portions that are consistent across influenza viruses, has informed the ongoing development of candidate "universal" influenza vaccines that may be given infrequently yet protect broadly against multiple influenza viruses. In addition, by comparing the 1918 virus to related influenza viruses found in animals, scientists have learned some of the changes necessary for influenza viruses to adapt from an animal to a human host. This has led to more targeted surveillance of certain influenza viruses in animals that may be more likely to move to humans.

More generally, the authors say that reconstruction of the 1918 influenza virus has furthered scientific understanding of how novel influenza viruses emerge and evolve. Additionally, study of the 1918 influenza virus has helped clarify the critical effects of the human immune system’s response to viral infection and the importance of bacterial co-infections that often follow the influenza infection. In sum, the authors write, learning more about the 1918 pandemic influenza virus has led to important insights that could help prevent or mitigate seasonal and pandemic influenza.

Article:

Gladstone scientists develop technique to decipher the dormant AIDS virus concealed in cells
Novel method could help advance the fight against persistent 'HIV latency'
SAN FRANCISCO, CA—September 11, 2012—Scientists at the Gladstone Institutes have gotten us one step closer to understanding and overcoming one of the least-understood mechanisms of HIV infection—by devising a method to precisely track the life cycle of individual cells infected with HIV, the virus that causes AIDS.

In a paper being published online today in Lab on a Chip, the laboratory of Gladstone Investigator Leor Weinberger, PhD, announced the development of a device that can pinpoint and track HIV inside CD4 T cells—the type of white blood cell that the AIDS virus targets. This development is particularly important for understanding "HIV latency," a state in which the virus goes dormant after the patient begins standard antiretroviral treatment. Current antiretroviral drugs do not kill HIV—they only keep it at bay—meaning that those with HIV must continue a lifetime of drug treatment so as not to develop AIDS. If they discontinue the drugs, the latent virus "wakes up" within just a few weeks and begins an onslaught against the body's immune system.

The breakthrough comes as the AIDS-researcher community is beginning to speak publicly about the possibility of curing HIV/AIDS. Understanding—and consequently interrupting—HIV latency is a key element in the effort to discover a cure for this devastating disease.

"HIV latency is perhaps the single greatest obstacle to eradicating HIV/AIDS in the 34 million people who live with the disease worldwide," said Dr. Weinberger, who is also an associate professor of biochemistry and biophysics at the University of California, San Francisco (UCSF), with which Gladstone is affiliated. "Existing techniques that try to uncover the cellular and viral mechanisms behind HIV latency are inefficient at studying very rare cells—and cells housing the latent HIV virus are one-in-a-million. Our technique presents a clear path towards understanding how HIV latency is regulated within a single cell, by tracking the individual cells that traditionally had been difficult to monitor."

Single-cell, time-lapse microscopy—a state-of-the-art technique that scientists have lately used to track some viral infections and map antibiotic resistance to drugs—has not worked for tracking the HIV-
infection cycle in CD4 T cells, especially in the latent state. This is because these cells are notoriously evasive. They spontaneously move around, attaching and detaching from their neighbors, making it nearly impossible to monitor individual HIV-infected cells over time.

However, Dr. Weinberger’s team devised a clever system that essentially guides and suspends HIV-infected T cells into tiny finger-like channels—reducing their ability to move or detach from their neighbors.

"First, we load the T cells into a small well, allowing them to settle into the bottom—which is filled with nutrients that keep the cells well-fed and stress-free," explained the paper’s lead author Brandon Razooky, a Gladstone and UCSF graduate student. "Next, we tilt the device and the cells slide into microscopic finger-like channels that are attached to the well. Finally, we return the device to its upright position, locking about 25 T cells inside each channel and essentially ‘freezing’ them in place."

The device has several advantages over current methods. First and foremost, individual cells stay in place so investigators can follow them over time with single-cell, time-lapse microscopy. Second, the fact that each T cell is suspended in nutrients in close physical contact with other cells results in near optimal conditions for keeping the infected cell alive for the virus’ entire life cycle.

"This means that we now have the potential to analyze the entire course of an HIV infection in an individual cell—especially during the crucial latency stage—for which we know so little,” said Dr. Weinberger. "In the future, we plan to expand the device’s design to include a larger number of wells and channels to track HIV infection on a larger scale. We want to use the information gleaned here to finally unravel the mechanisms behind HIV latency. With that knowledge, we hope to devise a treatment to bring the latent virus out of hiding in order to flush it from a patient’s system, once and for all."

**Powerful New Method for Finding Therapeutic Antibodies Devised: Technique Hones and Expands the Power of Large Numbers**

*ScienceDaily* (Sep. 11, 2012) — Scientists at The Scripps Research Institute have found a new technique that should greatly speed the discovery of medically and scientifically useful antibodies, immune system proteins that detect and destroy invaders such as bacteria and viruses. New methods to discover antibodies are important because antibodies make up the fastest growing sector of human therapeutics; it is estimated that by 2014 the top-three selling drugs worldwide will be antibodies.

The new technique, described in an article this week published online ahead of print by the journal *Proceedings of the National Academy of Sciences*, enables researchers to search large libraries of antibodies and quickly select the ones with a desired biological effect. It also provides for the creation of unusual, asymmetric antibodies whose capabilities extend beyond those of natural antibodies. The Scripps Research scientists demonstrated the power of the technique by using it to find an asymmetric antibody that almost perfectly mimics the activity of erythropoietin (EPO), a medically valuable hormone.

"Traditionally we’ve looked at antibodies as tools for binding to specific targets, but we should view them more generally, as tools for probing and altering functions in cells," said Richard Lerner, the Lita Annenberg Hazen Professor of Immunochemistry and member of the Department of Molecular Biology at Scripps Research who led the new study.

**At the Vanguard**

Lab-grown antibodies already represent a major part of the ongoing biotechnology revolution. Used as scientific probes or medical therapies, they recreate the versatility of natural antibodies, which are produced by immune cells in a vast diversity to bind to highly specific shapes on viruses, bacteria, and other targets.

Two decades ago, Lerner and his laboratory at Scripps Research, in parallel with the group of Sir Gregory Winter at the Laboratory of Molecular Biology in Britain, developed the first techniques for generating very large libraries of combinatorial antibodies and quickly isolating those that can bind to a desired target. Since then, such techniques have been used to find antibodies to treat cancer, arthritis, transplant rejection, and other conditions. Humira, an anti-inflammatory antibody that was discovered this way, is expected to be the world’s top-selling drug this year. Belimumab (Benlysta®) was approved by the US Food and Drug Administration in 2011 to treat lupus, becoming the first new drug to treat the chronic, life-threatening inflammatory disease in more than 50 years.

Current antibody-discovery techniques have one big drawback, however. Although they can rapidly find antibodies that bind tightly to a known target, they can’t rapidly determine which of those antibodies has useful biological activity. An antibody may bind tightly to a virus without affecting the virus’s ability to infect cells, for example, or it may bind to a cellular receptor without activating that receptor. With
current techniques, determining the overall biological effect of a target-binding antibody typically requires further, painstaking analysis.

**A More Direct Path**

In the new study, Lerner and his postdoctoral researcher Hongkai Zhang sought a method for rapidly finding antibodies that have a desired effect on cells, not just a desired ability to bind to a target. As a proof of principle, they aimed to discover an antibody that could mimic the activity of EPO, a hormone that stimulates red blood cell production. Drugs that mimic EPO’s effect are commonly used to treat anemia and related conditions.

Zhang began by using traditional techniques to quickly sift through a large antibody library to find tens of thousands of antibodies that bind tightly to the EPO receptor. He then stepped beyond traditional techniques, by taking the genes that encoded these EPO-receptor-binding antibodies and inserting them into lentiviruses. Unlike the phage viruses used in traditional methods, lentiviruses can usefully infect mammalian cells, delivering their payloads—antibodies, in this case—into a more human-like cellular environment.

Zhang applied this new library of antibody-coding lentiviruses to a single, large culture of mammalian test cells. The cells were of a type that express EPO receptors and proliferate when these receptors are bound by EPO proteins—or by antibodies that effectively mimic EPO. Each of these cells could host only a few viral particles at most, so in this way Zhang was able to distribute the entire library of EPO-receptor-binding antibodies broadly within the cell culture. Zhang also cultured the cells in a special way that prevented antibodies secreted by one cell from spreading easily to nearby cells and muddying any cause-effect relationship. "This concern over the diffusion of antibodies in the culture was one of the factors that had discouraged other researchers from using such a technique," said Zhang.

After the lentiviruses had delivered the antibodies to the cultured cells, Zhang was able to note which cells were proliferating the most—signifying the presence of antibodies that mimic EPO. To identify the antibodies responsible, Zhang had only to harvest these faster-growing cells and sequence the antibody genes inside them.

This method quickly yielded an antibody that in a further test showed about 60 percent of the biological activity of natural EPO—which was as good as any antibody EPO-mimic that had ever been described.

**Opening the Door to the Unknown**

But Zhang and Lerner also noted that many of the proliferating cells had been infected by multiple lentivirus particles, and contained sequences from more than one antibody. Puzzlingly, Zhang found that when he recreated antibodies from these sequences, and tested them individually or in combinations, they showed no significant EPO-mimicking effect. Further tests showed that the source of the EPO-mimicking effect in the test cells was an antibody that does not occur naturally.

An antibody of the type used in the study has a Y-shaped structure, normally with two identical binding arms. But the presence of multiple antibody genes within some of Zhang’s test cells meant that, in a few cases, antibodies assembled themselves with two different binding arms. One of these "bispecific" antibodies turned out to bind to the EPO receptor—which has two binding sites—in a way that very accurately mimics the binding of a natural EPO molecule. "It turned out to be 100 percent as potent as authentic EPO in further tests," Zhang said.

The serendipitous finding represents another major innovation, for, in principle, it extends the medical and scientific antibody repertoire from the 100 billion or so known variants of same-armed antibodies to an astronomically higher number of bispecific variants. Experiments to test such variants will be limited by the maximum number of usable cells in cultures, but that number is still very high, on the order of 10 million. "That allows for a lot of unique binding events," said Lerner. "You probably can get almost anything that way."

Lerner emphasizes that this new antibody-engineering/discovery technique can be used not just against known targets such as the EPO receptor, but also against cellular functions involving targets that have not yet been found. "The real power of this technique is its ability to help us discover the unknown," he said.

**Journal Reference:**

**Designer invents condom cover that can be opened with flick of a thumb**

Embarrassing fumbles in the dark could be over thanks to a one-handed condom wrapper.

Designer Ben Pawle has developed a cover that can be opened with the flick of a thumb.

The invention is about to go on show for the first time as industry experts try to get their hands on it.

‘Everyone has had a difficult wrapper at some point. It’s a bit of a mood killer,’ said Mr Pawle, 24.

‘I wanted to do something to relieve that undignified moment.’

He said the snap-open packet was inspired by the experiences of hemiplegics, who develop paralysis or weakness on one side of the body.

‘I wanted to do something that had a very human value,’ said Mr Pawle, who studied at Glasgow College of Art.

‘It’s a niche product but it can be used by anyone.’

The product goes on show at the Victoria and Albert Museum in London from Saturday.

**IPS Examines Controversy Over WHO-Approved Drug To Prevent Hemorrhage After Labor**

Inter Press Service examines the reaction to calls for the WHO "to reverse its listing in April 2011 of misoprostol among essential medicines that 'satisfy the health care needs of the majority of the population’ and are ‘available at all times in adequate amounts and in appropriate dosage forms, at a price the community can afford" as a result of a study published in the August issue of the Journal of the Royal Society of Medicine. "Originally intended for treating gastric ulcers, misoprostol has since 2000 been gaining in popularity for its ability to induce labor and stop postpartum hemorrhage (PPH),” according to the news service.

"Allyson Pollock [of Queen Mary, University of London], who led the study, stated that there is insufficient evidence to suggest that misoprostol works in preventing PPH" and instead "urges poor countries to improve primary care and prevent anemia to lower the risk of hemorrhage following delivery," IPS writes. "Pollock’s study has stirred international concern,” the news service notes, adding, "International Planned Parenthood Federation's Upeka de Silva told IPS in an e-mail that if WHO withdraws misoprostol, it would mean 'countless women will be denied life-saving care and forced to suffer pregnancy-related complications which are entirely preventable'" (Ebrahim, 9/12).

**Gut bacteria increase fat absorption**

Baltimore, MD —You may think you have dinner all to yourself, but you're actually sharing it with a vast community of microbes waiting within your digestive tract. A new study from a team including Carnegie's Steve Farber and Juliana Carten reveals that some gut microbes increase the absorption of dietary fats, allowing the host organism to extract more calories from the same amount of food.

Previous studies showed gut microbes aid in the breakdown of complex carbohydrates, but their role in dietary fat metabolism remained a mystery, until now. The research is published September 13 by *Cell Host & Microbe*.

"This study is the first to demonstrate that microbes can promote the absorption of dietary fats in the intestine and their subsequent metabolism in the body," said senior study author John Rawls of the University of North Carolina. "The results underscore the complex relationship between microbes, diet and host physiology."

The study was carried out in zebrafish, which are optically transparent when young. By feeding the fish fatty acids tagged with fluorescent dyes, an approach originally developed in Farber's lab, the researchers were able to directly observe the absorption and transport of fats in live animals. The Rawl's lab pioneered methods to grow zebrafish larvae in the presence or absence of gut microbes.

By combining approaches, they determined that one type of bacteria, called Firmicutes, is instrumental in increasing fat absorption. They also found that the abundance of Firmicutes in the gut was influenced by diet. Fish fed normally had more Firmicutes than fish that were denied food for several days. Other studies have linked a higher relative abundance of Firmicutes in the gut with obesity in humans.

The findings indicate that bacteria in the gut can increase the host's ability to absorb fat and thereby harvest more calories from the diet. Another implication is that a high-fat diet promotes the growth of these fat-loving Firmicutes, resulting in more fat absorption.

Although the study involved only fish, not humans, it offers insights that could help inform new approaches to treating obesity and other disorders.
“The unique properties of zebrafish larvae are helping us develop a better understanding of how the intestine functions with the goal of contributing to ongoing efforts to reduce the impact of diseases associated with altered lipid metabolism, such as diabetes, obesity, and cardiovascular disease. Our collaboration with the Rawls lab is now focused on how specific gut bacteria are able to stimulate absorption of dietary fat. We hope to use that information to develop new ways to reduce fat absorption in the context of human diseases,” Farber said.

Sinusitis linked to microbial diversity
UCSF study suggests new approach for dealing with common ailment
A common bacteria ever-present on the human skin and previously considered harmless, may, in fact, be the culprit behind chronic sinusitis, a painful, recurring swelling of the sinuses that strikes more than one in ten Americans each year, according to a study by scientists at the University of California, San Francisco.

The team reports this week in the journal *Science Translational Medicine* that sinusitis may be linked to the loss of normal microbial diversity within the sinuses following an infection and the subsequent colonization of the sinuses by the culprit bacterium, which is called *Corynebacterium tuberculostearicum*.

In their study, the researchers compared the microbial communities in samples from the sinuses of 10 patients with sinusitis and from 10 healthy people, and showed that the sinusitis patients lacked a slew of bacteria that were present in the healthy individuals. The patients also had large increases in the amount of *Corynebacterium tuberculostearicum* in their sinuses, which are located in the forehead, cheeks and eyes.

The team also identified a common bacterium found within the sinuses of healthy people called *Lactobacillus sakei* that seems to help the body naturally ward off sinusitis. In laboratory experiments, inoculating mice with this one bacterium defended them against the condition.

"Presumably these are sinus-protective species," said Susan Lynch, PhD, an associate professor of medicine and director of the Colitis and Crohn's Disease Microbiome Research Core at UCSF.

What it all suggests, she added, is that the sinuses are home to a diverse "microbiome" that includes protective bacteria. These "microbial shields" are lost during chronic sinusitis, she said, and restoring the natural microbial ecology may be a way of mitigating this common condition.

A Painful, Costly Condition
Sinuses are air-filled cavities in the front of the skull that connect to the nasal passages and are lined with mucosal surfaces. They are somewhat shrouded in mystery. Scientists are not entirely sure what they do. They may exist to heat air as it passes into the body, they may be associated with the immune system, or as Lynch and her colleagues speculate, they may represent a site of microbial surveillance just inside the nose where the body can sample bacteria and other microbes entering the body.

Though the sinuses’ underlying purpose is still unclear, they are all too familiar to American doctors and their patients because of what happens when the thin tissues lining them become inflamed, as occurs in chronic sinusitis—one of the most common reasons why people go to the doctor in the United States. There are about 30 million cases each year, and the cost to the healthcare system is an estimated $2.4 billion dollars annually.

The pain of sinusitis can last for months. Doctors typically prescribe bacteria-killing antibiotics and, in more severe and long-lasting cases, conduct sinus surgeries. However, said Andrew Goldberg, MSCE, MD, the director of rhinology and sinus surgery at UCSF and a co-author on the paper, "the premise for our understanding of chronic sinusitis and therapeutic treatment appears to be wrong, and a different therapeutic strategy seems appropriate."

The new work suggests that if the underlying cause of sinusitis is due to changes to the microbiome of bacterial species colonizing sinus tissue, restoring the naturally-occurring, protective bacteria to these cavities may be an effective way to treat this condition.

However, the UCSF-led team warned that the promise of this discovery does not offer an immediate new treatment or cure for sinusitis. Any new approaches based on these observations still have to be developed and tested for safety and effectiveness in human clinical trials.

'Berlin Man,' Doctor Convinced HIV Cure Is Real

The first person reportedly cured of HIV said Wednesday he is hopeful that medical advances will allow others suffering from the virus that causes AIDS to be cured, too.

Timothy Ray Brown of San Francisco is known as "The Berlin Patient" because of where he was treated. He and the doctor who treated him, Gero Hutter, made their first joint appearance in the U.S. on Wednesday when Hutter spoke at a symposium on gene therapy at Washington University in St. Louis.

Scientists are studying whether gene therapy can be used to rid the body of HIV. Some doctors remain skeptical that Brown, 46, is cured. His case was first reported in the media in 2008 and described in the New England Journal of Medicine in 2009.

Brown and Hutter, in an interview with The Associated Press during the symposium, said the passage of time is further proof that Brown is cured. Hutter cited the same five-year standard after which some cancer patients are said to be cured.

Brown was diagnosed with HIV in 1995. In 2006, he also developed leukemia while living in Germany. Hutter performed a blood stem cell transplant using a donor with a rare gene mutation that provides natural resistance to HIV. Hutter said that resistance transferred to Brown.

Brown said he feels great, has not needed HIV medication since the 2007 surgery, and is now active in a foundation named for him that seeks a cure for HIV.

Brown grew up in Seattle and moved to Germany in 1993. After the HIV diagnosis, he started on medication to prevent him from developing full-blown AIDS.

He was attending a wedding in New York in 2006 when he became unusually tired. An avid cyclist, within weeks he could barely ride the bike and eventually was diagnosed with leukemia.

Brown underwent chemotherapy but needed a blood stem cell transplant and turned to Hutter, a blood specialist at Heidelberg University.

Hutter suggested they seek a donor with a certain cell feature that gives them natural resistance to HIV infection. Only about 1 percent of the northern European population has this feature. Hutter theorized that a transplant from such a donor could make the recipient resistant to HIV.

Hutter said no one apparently had tried this, and his idea received mixed reaction from other doctors. "Some were very excited, but many were skeptical," he said.

But within weeks, Hutter said, tests showed promise that Brown was cured.

"I don't know if I really believed it was cured" until the case was described in the New England Journal of Medicine, Brown said.

Earlier this year, doctors in California found traces of HIV in Brown's tissue, leading to speculation that the disease had returned. But Hutter said the traces are remnants of the disease that can't replicate or cause a recurrence.

The symposium in St. Louis was hosted by the university's Biologic Therapeutics Center, which seeks to advance the use of gene therapy. Speakers said gene therapy has helped treat cancer, hemophilia and other diseases.

So far, Brown is the only person believed to have been cured of HIV. Hutter began procedures in 2008 with 12 other people who had both HIV and cancer, but some were too sick to undergo treatment, and others couldn't find matching donors or ran into other roadblocks.

Booster HIV Drug Can Be Dropped

This report is part of a 12-month Clinical Context series.

By Michael Smith, North American Correspondent, MedPage Today

Published: September 12, 2012

Reviewed by Robert Jasmer, MD; Associate Clinical Professor of Medicine, University of California, San Francisco and Dorothy Caputo, MA, BSN, RN, Nurse Planner

SAN FRANCISCO—A simplified HIV regimen that omits the booster drug ritonavir (Norvir) can effectively maintain viral suppression, a researcher said here.

In a randomized trial, switching away from the booster drug allowed treatment-experienced patients to keep HIV under control and reduced toxicity, according to David Wohl, MD, of the University of North Carolina in Chapel Hill.

The switch also improved some important biomarkers, Wohl said in a late-breaker presentation at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.
The so-called ASSURE trial enrolled 296 patients whose serum viral load was less than 75 copies of HIV RNA per milliliter on a standard regimen of tenofovir and emtricitabine (Truvada), coupled with ritonavir-boosted atazanavir (Reyataz).

Two-thirds of them were switched to abacavir and lamivudine (Epzicom), coupled with unboosted atazanavir and the whole group was followed for 48 weeks. Ritonavir, a protease inhibitor, is used primarily to boost the pharmacokinetic properties of other drugs but it adds toxicities to any regimen in which it is included.

The primary goal of the study was to see if the two regimens were non-inferior after 24 weeks in terms of their ability to suppress serum viral load to below 50 copies of HIV RNA per mL.

But the researchers also measured effects on the immune system, adverse events, and changes in lipids.

After 24 weeks, 86.9% of those on the simplified regimen had met the primary goal, compared with 86.6% of those on their original drugs, Wohl reported.

The 0.33 percentage point difference had a 95% confidence interval from -7.97% to 8.64% and was well within the 12-percentage point margin of inferiority, he noted.

Wohl said he and colleagues also found an increase in the number of CD4-positive T cells for those on the simplified regimen that was significantly greater (at $P=0.013$) at 24 weeks than for those on the original regimen that included ritonavir.

They also noted a significant difference (at $P<0.001$) in emergent or worsening laboratory adverse events that favored the simplified regimen. The difference was driven by higher bilirubin levels among those on the ritonavir-containing regimen.

There was a significant decline (at $P<0.001$) in B2 microglobulin/creatinine ratio among those who switched to the simpler regimen, but no change among those who continued their original program. The between-group difference was also significant ($P<0.001$).

Also, there was a significant decline in biomarkers of bone turnover (at $P<0.001$ for all measured markers) among those who switched, but no change among patients who remained on the ritonavir-containing regimen. The between-group differences were also significant ($P<0.001$).

There were similar rates of grades 2 through 4 clinical adverse events and adverse events that led patients to stop therapy.

Finally, fasting lipid profiles remained "very much stable" despite the switch in regimens.

The study provides a rationale for a relatively common practice, commented Douglas Ward, MD, of the Dupont Circle Physician's Group in Washington, D.C., who was not involved in the study but who moderated the ICAAC session at which it was presented.

"Personally, that's the approach I've been taking for quite some time," he told MedPage Today. "I get people undetectable on a ritonavir-containing regimen and then drop the ritonavir."

That simplifies the regimen, he said, and can "potentially reduce toxicity" associated with ritonavir.

The newly developed pharmacokinetic booster, cobicistat, is likely to have less toxicity than ritonavir, he noted, but it too will have drug-drug interactions that will prompt physicians to try to avoid it.

Cobicistat is currently awaiting an FDA decision on approval.

Long-Lasting HIV Drug Could Change Therapy

This report is part of a 12-month Clinical Context series.
By Michael Smith, North American Correspondent, MedPage Today
Published: September 12, 2012
Reviewed by Robert Jasmer, MD; Associate Clinical Professor of Medicine, University of California, San Francisco and Dorothy Caputo, MA, BSN, RN, Nurse Planner

SAN FRANCISCO – An extremely long-lasting anti-HIV drug has the potential to alter both treatment and prevention of the virus, researchers said here.

Preliminary data presented at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy suggest that the investigational integrase inhibitor S/GSK744 might need to be given only every 3 months.

That would have "enormous implications for treatment, but perhaps even more for prevention," said Roy Gulick, MD, of Weill Cornell Medical College in New York City, who was not involved in the research.

Currently, the most convenient treatments are one-pill, once-daily combinations of three drugs, and pre-exposure prophylaxis (PrEP) that involves taking a single medication daily.
Treatment would likely still have to involve three drugs, so that the long-lasting S/GSK744 would be just a part of a complete regimen. But the FDA has recently approved the single-pill combination of tenofovir and emtricitabine (Truvada) – taken daily – as a PrEP option for people at high risk of HIV infection.

A "drug that hung around for 3 months" would be an even more attractive approach to prevention, Gulick told MedPage Today.

S/GSK744 when given orally has a plasma half-life of about 30 hours, according to Tomokazu Yoshinaga, PhD, of Shionogi in Osaka, Japan, which is developing the compound in collaboration with GlaxoSmithKline.

But when a single dose is given by injection – either subcutaneously or into muscle – the drug can be detected for as long as 48 weeks, he reported.

What's causing the excitement is that levels of the drug remained above the protein-adjusted 90% inhibitory concentration for 12 weeks at all but the lowest dose tested.

In addition, Yoshinaga reported, the drug is active against a broad range of HIV subtypes as well as HIV-2, has limited cross-resistance with other integrase inhibitors, and has a high barrier to resistance in lab experiments.

In an early clinical test, the oral formulation, given as monotherapy, led to a rapid decline of up to 2.5 log10 copies of HIV RNA per milliliter of blood in a small number of patients.

Taken together, the data suggest that the compound "may have a favorable profile for both HIV treatment and PrEP," he concluded.

The report on S/GSK744 was one of three studies here that presented early data on new drugs for HIV. Also under discussion were an analog of the nucleotide analog reverse transcriptase inhibitor tenofovir (Viread) that is thought to be more potent and perhaps less toxic, as well as a new non-nucleoside reverse transcriptase inhibitor.

Tenofovir is a nucleotide reverse transcriptase inhibitor that is concerted within cells to its active metabolite, tenofovir diphosphate. The oral prodrug tenofovir disoproxil fumarate (Viread) is widely used as part of HIV treatment.

A novel tenofovir prodrug—tenofovir alafenamide, or Taf—is more potent than Viread, according to Christian Callebaut, PhD, of Gilead Sciences in Foster City, Calif., which is developing the compound. The compound, also known as GS-7340, has greater antiviral activity at lower doses than its older counterpart, Callebaut said.

The substance also is active against a broad range of HIV isolates, as well as the less common virus HIV-2, he reported, and appears to have synergistic or additive effects when combined with other antiretroviral drugs.

The drug has been through phase I trials and is now in phase II, so more clinical data may be coming soon, Gulick commented.

Interest in the drug has been piqued by the additional potency: "You can use [fewer] milligrams and get more antiviral effect," he said.

One possible implication is that the compound will have fewer side effects than its older counterpart, Gulick said, "but they haven't shown that yet."

Finally, preclinical data on a new non-nucleoside reverse transcriptase inhibitor, dubbed MK-1439, show it appears to be both potent and active against many drug-resistant HIV strains, according to Ming-Tain Lai, PhD, of Merck in West Point, Pa., which is developing the compound.

The compound retained activity against a range of commonly transmitted resistance mutations that affect the drug class and often rendered other non-nucleoside reverse transcriptase inhibitors less useful, Lai reported.

But HIV strains containing one resistance mutation – dubbed Y188L – resulted in more than a 100-fold increase in the 50% inhibitory concentration, Lai said.

"Any time you have a single mutation that can knock off the drug, that's a concern," Gulick commented.

The compound is currently in phase II studies, but Lai said he had no data on how well those are progressing.
New analysis in Science tells how world eradicated deadliest cattle plague
deadliest cattle plague
2nd such success after smallpox; Authors reveal essential role of Africa's nomadic herders
in ridding the world of rinderpest; lessons learned vital to battling livestock diseases
currently devastating developing world
NAIROBI, KENYA (13 September 2012)—A new analysis published today in Science traces the recent
global eradication of the deadliest of cattle diseases, crediting not only the development of a new, heat-resistant vaccine, but also the insight of local African herders, who guided scientists in deciding which animals to immunize and when. The study provides new insights into how the successful battle against rinderpest in Africa, the last stronghold of the disease, might be applied to similar diseases that today ravage the livestock populations on which the livelihoods of one billion of the world's poor depend.

"The elimination of rinderpest is an enormous triumph against a disease that has plagued animals and humankind for centuries," said Jimmy Smith, director general of the International Livestock Research Institute (ILRI). "Science succeeded despite limited resources, and we now know how. We are committed to applying the lessons in this study to making progress against other similarly destructive livestock diseases."

According to the analysis, which was conducted by international scientists coordinated by ILRI, and published this week in Science, the eradication of rinderpest happened thanks to the development of an effective temperature-stable vaccine, collaborations between veterinary health officials and cattle farmers to deliver those vaccines, and reliance on the knowledge and expertise of the local herders to determine the location and movement of outbreaks.

The cattle plague and its path of destruction
Rinderpest, known as "cattle plague" in English, is thought to have had its origin in the dense cattle herds of Central Eurasia more than two millennia ago and subsequently spread through warfare and trade to cattle in Europe, Asia and eventually Africa. Caused by a virus related to the one that causes measles and canine distemper, rinderpest could infect cows, water buffalos and other cloven-hoofed animals, leading to a high fever, severe diarrhea, then dehydration and emaciation. The pathogen could kill 90 percent of a herd, wiping out an entire farm's livestock in just a matter of days. There was no treatment.

While rinderpest is not dangerous to human health, its impact on humanity has been significant. Its path of destruction has been linked to many history-changing events such as the fall of the Roman Empire, the French Revolution and famines throughout Africa since the 19th century. Indeed, nearly three-quarters of the rural poor and some one-third of the urban poor depend on livestock for their food, income, traction, manure or other services. Livestock provide poor households with up to half their income and between 6 and 35 percent of their protein consumption. The loss of a single milking animal can affect a family's economic health, while depriving it of a primary source of nutrition.

Road to eradication
The first major contributing factor to eradication, as identified by the analysis, was a major improvement made to an existing rinderpest vaccine. While the original vaccine was safe, effective, affordable, and easy to produce, it needed to be refrigerated—making it nearly impossible to transport it to remote rural villages. With the development of a new heat-resistant vaccine formulation in 1990 that could be stored at 37°C for eight months, and in the field without refrigeration for 30 days, scientists had a tool that would become the cornerstone of the eradication effort in remote pastoral areas of Africa.

But according to ILRI’s Jeffrey Mariner, the analysis' lead author and inventor of the temperature-stable rinderpest vaccine, it was the role played by pastoralists that really turned rinderpest on its head.

As part of a public-private-community partnership, Mariner and colleagues trained what they called community-based animal health workers, or CAHWs—local pastoralists who were willing to travel on foot and able to work in remote areas—on how to deliver the new vaccine. These CAHWs carried the vaccine from herd to herd, immunizing all the cattle in their communities.

The local herders performed as well, if not better, than did veterinarians at vaccinating the herds—in fact often achieving higher than 80 percent herd immunity in a short time—remarkable for a disease that had plagued most of the world for millennia. Indeed, it turned out that the pastoralists were not only very, very good at delivering the vaccine, but that they also knew more about the disease and how to stop it than many of the experts.
"We soon discovered that the livestock owners knew more than anyone—including government officials, researchers or veterinarians—where outbreaks were occurring," Mariner said. "It was their expertise about the sizes of cattle herds, their location, seasonal movement patterns and optimal time for vaccination that made it possible for us to eradicate rinderpest."

Based on their immense expertise about migratory patterns and in recognizing early signs of infection, the herders were able to pinpoint, well before scientists ever could, where some of the final outbreaks were occurring—often where conventional surveillance activities had failed to disclose disease. Harnessing this knowledge of rinderpest through "participatory surveillance" of outbreaks to CAHW delivery of vaccination proved to be the most successful approach to monitoring and controlling the disease. It effectively removed the disease from some of the hardest-to-reach, but also most disease-ridden, communities.

**Applying rinderpest lessons to other diseases**

While livestock and those who depend on them for food, transportation and economic stability are now safe from one major pathogen, they continue to be plagued by a number of other dangerous and debilitating diseases—some as deadly as rinderpest.

The international animal health community is now gearing up to address the next major constraint to livestock livelihoods in Africa and Asia. In their analysis, Mariner and colleagues consider how the lessons learned from battling rinderpest can be applied to protect livestock from other infectious agents—particularly peste des petits ruminants (PPR), also known as "goat plague." Strategies to address PPR using the lessons from rinderpest have been developed and action is underway to mobilize international support for a coordinated program to tackle PPR. As a next step, ILRI and the Africa Union/Interafrican Bureau for Animal Resources are planning to host the next meeting of the PPR Alliance, a partnership of research and development organizations who prioritize PPR, in Nairobi in early 2013.

A dangerous virus that can destroy whole flocks of sheep and goats, PPR threatens livestock owners in Africa, Asia and the Middle East, in particular. As with rinderpest, a sheep or goat infected with PPR will come down with a high fever and will stop eating, leading to severe diarrhea and death. Eventually, it will take down the entire herd of the animals, which are equal to cattle in their importance to the poor. And controlling PPR is made challenging by the short life span and heavy trading of sheep and goats—making it difficult to keep the disease in check and preventing its spread to new areas.

Nonetheless, the lessons of rinderpest eradication have begun to have an impact on the toll exacted by goat plague. Participatory surveillance methods are now applied in many countries, CAHWs are now frequently involved in vaccination campaigns and ILRI has developed a temperature-stable vaccine that can be transported to rural farms and has started to put into place training programs for shepherds and farmers in Uganda and Sudan to deliver it.

Eventually, these same lessons could be applied to other livestock diseases such as foot-and-mouth disease—even some that have recently jumped to humans, like avian flu. Such "zoonotic" diseases are responsible for 2.4 billion cases of human illness and 2.2 million deaths per year, primarily in low- and middle-income countries.

**Immune system compensates for 'leaky gut' in inflammatory bowel disease susceptibility**

New research could clarify how inflammatory bowel diseases (IBD), conditions that include ulcerative colitis and Crohn's disease, are triggered and develop.

Scientists at Emory University School of Medicine have shown how the immune system can compensate for a "leaky gut" and prevent disease in mice that are susceptible to intestinal inflammation. These findings could explain why some individuals who are susceptible to developing IBD do or do not get the disease.

The results will be published online Sept. 13 in the journal *Immunity*.

"Our results suggest that when there is a chronically leaky intestine, defects in the immune system need to be present for the development of IBD," says senior author Charles Parkos, MD, PhD, professor of pathology and laboratory medicine at Emory University School of Medicine.

"Breakdown of the intestinal barrier can occur as a result of intestinal infections or stress. The normal response involves several components of the immune system that help to heal the injury while controlling invading bacteria. When this normal response is defective and there is a leaky barrier, the risk of developing IBD is increased."
Parkos and co-senior author Tim Denning, PhD, assistant professor of pediatrics, and their colleagues have been studying mice that are deficient in a protein called JAM-A (junctional adhesion molecule A). JAM-A is an important regulator of the epithelial barrier in the intestine. Denning describes JAM-A and other “tight junction” molecules as forming a seal between epithelial cells like a zipper, which keeps bacteria away from the rest of the body.

JAM-A deficient mice have a “leaky gut,” meaning that chemicals and bacteria can cross more easily from the insides of the intestines to the rest of the body. Passage of bacteria across the intestinal wall and into the body can cause inflammation and disease. JAM-A deficient mice have more bacteria in the liver and lymph nodes, and they are more susceptible than regular mice to a chemical treatment (DSS) that induces colitis (intestinal inflammation). Surprisingly, despite these defects, JAM-A deficient mice do not develop spontaneous colitis.

“This is a situation that may be analogous to first degree relatives of people with Crohn’s disease,” Parkos says. “Some of these people have increased intestinal permeability, which suggests that they are more susceptible to developing disease, but they don’t get sick. Gut permeability also transiently increases in normal people based on what we eat and drink, yet disease doesn’t occur. We think that immune compensation is what protects the body under these conditions.”

The researchers wanted to dissect which types of immune cells were responsible for this compensatory effect. To this end, they treated JAM-A deficient mice with antibodies that depleted certain types of immune cells or, in some cases, examined mice with additional genetic changes in combination with the JAM-A deficiency. They found that a type of immune cell, CD4+ T cells, is needed to produce signals that encourage production of a type of antibody, IgA. IgA is especially important for limiting incursions by bacteria in the intestine.

“In normal mice, immune cells such as CD4+ T cells and IgA-producing B cells do not play a big role in DSS-triggered colitis,” Denning says. “But if the mice have a preexisting leak, the immune system plays an important role.”

Under normal conditions, B cells are needed to produce IgA, which helps to keep bacteria from invading through the intestinal wall. While defects in the production of IgA alone do not result in colitis, the presence of a chronically leaky gut in concert with IgA deficiency results in increased susceptibility to abnormal intestinal inflammation that involves other types of immune cells. During intestinal inflammation, the amount of JAM-A in the epithelium can decrease, thus further weakening the intestinal barrier.

“There is a ‘chicken or the egg’ question with respect to whether inflammation or alterations in the intestinal barrier come first,” Parkos says. “Many people with IBD report that their first severe episode was brought on by a stressful event or an intestinal illness, and it is possible that these events serve as a trigger that starts a vicious cycle of altered barrier and inflammation.”

**Laser-powered ‘needle’ promises pain-free injections**

**Optical technology gives a sci-fi twist to traditional medicine**

WASHINGTON, Sept. 13—From annual flu shots to childhood immunizations, needle injections are among the least popular staples of medical care. Though various techniques have been developed in hopes of taking the “ouch” out of injections, hypodermic needles are still the first choice for ease-of-use, precision, and control.

A new laser-based system, however, that blasts microscopic jets of drugs into the skin could soon make getting a shot as painless as being hit with a puff of air.

The system uses an erbium-doped yttrium aluminum garnet, or Er:YAG, laser to propel a tiny, precise stream of medicine with just the right amount of force. This type of laser is commonly used by dermatologists, “particularly for facial esthetic treatments,” says Jack Yoh, professor of mechanical and aerospace engineering at Seoul National University in South Korea, who developed the device along with his graduate students. Yoh and his team describe the injector in a paper published today in the Optical Society’s (OSA) journal *Optics Letters*.

The laser is combined with a small adaptor that contains the drug to be delivered, in liquid form, plus a chamber containing water that acts as a “driving” fluid. A flexible membrane separates these two liquids. Each laser pulse, which lasts just 250 millionths of a second, generates a vapor bubble inside the driving fluid. The pressure of that bubble puts elastic strain on the membrane, causing the drug to be forcefully ejected from a miniature nozzle in a narrow jet a mere 150 millionths of a meter (micrometers) in diameter, just a little larger than the width of a human hair.
“The impacting jet pressure is higher than the skin tensile strength and thus causes the jet to smoothly penetrate into the targeted depth underneath the skin, without any splashback of the drug,” Yoh says. Tests on guinea pig skin show that the drug-laden jet can penetrate up to several millimeters beneath the skin surface, with no damage to the tissue. Because of the narrowness and quickness of the jet, it should cause little or no pain, Yoh says. "However, our aim is the epidermal layer," which is located closer to the skin surface, at a depth of only about 500 micrometers. This region of the skin has no nerve endings, so the method "will be completely pain-free," he says.

In previous studies, the researchers used a laser wavelength that was not well absorbed by the water of the driving liquid, causing the formation of tiny shock waves that dissipated energy and hampered the formation of the vapor bubble. In the new work, Yoh and colleagues use a laser with a wavelength of 2,940 nanometers, which is readily absorbed by water. This allows the formation of a larger and more stable vapor bubble "which then induces higher pressure on the membrane," he explains. "This is ideal for creating the jet and significantly improves skin penetration."

Although other research groups have developed similar injectors, "they are mechanically driven," using piston-like devices to force drugs into the skin, which gives less control over the jet strength and the drug dosage, Yoh says. "The laser-driven microjet injector can precisely control dose and the depth of drug penetration underneath the skin. Control via laser power is the major advancement over other devices, I believe."

Yoh is now working with a company to produce low-cost replaceable injectors for clinical use. "In the immediate future, this technology could be most easily adopted to situations where small doses of drugs are injected at multiple sites," he says. "Further work would be necessary to adopt it for scenarios like mass vaccine injections for children."


---

**Mutation Breaks HIV’s Resistance to Drugs, Says MU Researcher***

**Doctors can improve treatment programs using this knowledge**

Sept. 13, 2012

**Story Contact(s):** Timothy Wall, walltj@missouri.edu, 573-882-3346

COLUMBIA, Mo. – The human immunodeficiency virus (HIV) can contain dozens of different mutations, called polymorphisms. In a recent study an international team of researchers, including MU scientists, found that one of those mutations, called 172K, made certain forms of the virus more susceptible to treatment. Soon, doctors will be able to use this knowledge to improve the drug regimen they prescribe to HIV-infected individuals.

“The 172K polymorphism makes certain forms of HIV less resistant to drugs,” said Stefan Sarafianos, corresponding author of the study and researcher at MU’s Bond Life Sciences Center. “172K doesn’t affect the virus’ normal activities. In some varieties of HIV that have developed resistance to drugs, when the 172K mutation is present, resistance to two classes of anti-HIV drugs is suppressed. We estimate up to 3 percent of HIV strains carry the 172K polymorphism.”

HIV is a retrovirus, meaning it uses an enzyme called reverse transcriptase to create copies of its own genetic code. These copies are inserted into the victim’s own genes where the virus highjacks the host’s cellular machinery in order to reproduce itself. Two classes of drugs, nucleoside (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), can stop this process in its tracks.

However, some HIV strains have developed resistance to NRTIs and NNRTIs. The 172K polymorphism suppresses this resistance and allows both classes of drugs to fight HIV more efficiently. The mutation is believed to be the first of its kind that blocks resistance to two families of drugs.
“Clinical doctors use a database of HIV mutations and the drugs they are susceptible to when they prescribe treatments to an HIV-infected patient,” Sarafianos said. “Our finding will be integrated into this database. Once that happens, when doctors learn that their patients have HIV strains that carry the 172K polymorphism, they will know that the infections can be fought better with NRTIs and NNRTIs.”

One of Sarafianos’ colleagues at the AIDS Clinical Center in Japan found the 172K polymorphism by accident. The mutation was first discovered in a patient, and the researchers were able to recreate it in the laboratory.

The study “HIV-1 Reverse Transcriptase Polymorphism 172K Suppresses the Effect of Clinically Relevant Drug Resistance Mutations to Both Nucleoside and Nonnucleoside RT Inhibitors,” was published in the Journal of Biological Chemistry. The lead author was Atsuko Hachiya of the AIDS Clinical Center at Japan’s National Center for Global Health and Medicine in Tokyo. Stefan Sarafianos is associate professor of molecular microbiology & immunology in the MU School of Medicine and associate professor of biochemistry in the College of Arts and Science. Sarafianos also is associated with the Bond Life Science Center.

**Study of Giant Viruses Shakes Up Tree of Life**

Giant viruses should be included reconstructions of the tree of life, researchers report in a new study. The mimivirus, shown here...
A new study of giant viruses supports the idea that viruses are ancient living organisms and not inanimate molecular remnants run amok, as some scientists have argued. The study may reshape the universal family tree, adding a fourth major branch to the three that most scientists agree represent the fundamental domains of life.

The new findings appear in the journal *BMC Evolutionary Biology*.

The researchers used a relatively new method to peer into the distant past. Rather than comparing genetic sequences, which are unstable and change rapidly over time, they looked for evidence of past events in the three-dimensional, structural domains of proteins. These structural motifs, called folds, are relatively stable molecular fossils that—like the fossils of human or animal bones—offer clues to ancient evolutionary events, said University of Illinois crop sciences and Institute for Genomic Biology professor Gustavo Caetano-Anollés, who led the analysis.

"Just like paleontologists, we look at the parts of the system and how they change over time," Caetano-Anollés said. Some protein folds appear only in one group or in a subset of organisms, he said, while others are common to all organisms studied so far.

"We make a very basic assumption that structures that appear more often and in more groups are the most ancient structures," he said.

Most efforts to document the relatedness of all living things have left viruses out of the equation, Caetano-Anollés said. "We've always been looking at the Last Universal Common Ancestor by comparing cells," he said. "We never added viruses. So we put viruses in the mix to see where these viruses came from."

The researchers conducted a census of all the protein folds occurring in more than 1,000 organisms representing bacteria, viruses, the microbes known as archaea, and all other living things. The researchers included giant viruses because these viruses are large and complex, with genomes that rival—and in some cases exceed—the genetic endowments of the simplest bacteria, Caetano-Anollés said.

"The giant viruses have incredible machinery that seems to be very similar to the machinery that you have in a cell," he said. "They have complexity and we have to explain why."

Part of that complexity includes enzymes involved in translating the genetic code into proteins, he said. Scientists were startled to find these enzymes in viruses, since viruses lack all other known protein-building machinery and must commandeer host proteins to do the work for them.

In the new study, the researchers mapped evolutionary relationships between the protein endowments of hundreds of organisms and used the information to build a new universal tree of life that included viruses. The resulting tree had four clearly differentiated branches, each representing a distinct "supergroup." The giant viruses formed the fourth branch of the tree, alongside bacteria, archaea and eukarya (plants, animals and all other organisms with nucleated cells).

The researchers discovered that many of the most ancient protein folds—those found in most cellular organisms—were also present in the giant viruses. This suggests that these viruses appeared quite early in evolution, near the root of the tree of life, Caetano-Anollés said.

The new analysis adds to the evidence that giant viruses were originally much more complex than they are today and experienced a dramatic reduction in their genomes over time, Caetano-Anollés said. This reduction likely explains their eventual adoption of a parasitic lifestyle, he said. He and his colleagues suggest that giant viruses are more like their original ancestors than smaller viruses with pared down genomes.

The researchers also found that viruses appear to be key "spreaders of information," Caetano-Anollés said.

"The protein structures that other organisms share with viruses have a particular quality, they are (more widely) distributed than other structures," he said. "Each and every one of these structures is an incredible discovery in evolution. And viruses are distributing this novelty," he said.

Most studies of giant viruses are "pointing in the same direction," Caetano-Anollés said. "And this study offers more evidence that viruses are embedded in the fabric of life."

**Journal Reference:**

Epigenetics Emerges Powerfully as a Clinical Tool
ScienceDaily (Sep. 12, 2012) — A study coordinated by Manel Esteller, published in Nature Reviews Genetics, highlights the success of epigenetics to predict the behavior and weaknesses of tumors.

The research team led by Manel Esteller, director of the Cancer Epigenetics and Biology Program at the Bellvitge Biomedical Research Institute (IDIBELL), professor of genetics at the University of Barcelona and ICREA researcher, has updated the latest findings in applied epigenetic in a review paper published in Nature Reviews Genetics.

There is a growing need for better biomarkers that allow early detection of human diseases, especially cancer. The markers can improve primary prevention, diagnosis and prognosis of disease. Furthermore, it is possible to predict which may be more effective treatments according to patient characteristics, which is known by the name of personalized medicine.

The genetic tests complementary to traditional methods have been used to improve the approach to various diseases, but in the last ten years epigenetics has hardly emerged to help solve these clinical situations, as highlighted by the article. Epigenetics is the discipline for the study of the chemical changes in our genetic material and the same regulatory proteins. The most known epigenetic mark is the addition of a methyl group to the DNA.

The paper notes that the last decade two tests based on the methylation of two genes, MGMT and GSTP1, have been proved vital in predicting brain tumors sensitive to the temozolomide drug and in distinguishing prostate cancer compared benign growth, respectively. Dr. Esteller points out that "the most exciting thing is that they are currently being identified new epigenetic biomarkers for predicting the performance and weaknesses of tumors at a fast pace." In this sense, the coordinator of the study cites the recent identification of epigenetic alterations in predictive genes as response to new generation drugs in leukemia and the fact that obtaining a "picture" of the DNA methylation pattern can expose unknown tumors that previously had a very poor prognosis.


Flu Fights Dirty
Mimicking a host-cell histone protein offers flu a sneaky tactic to suppress immune response.

By Hayley Dunning | September 1, 2012
HOST PROTEIN IMPERSONATOR: The Hong Kong flu virus depicted here is one strain of the H3N2 subtype of influenza A, which carries a histone mimic that prevents host cells from producing antiviral proteins. Kallista Images

EDITOR'S CHOICE IN MICROBIOLOGY

The paper

The finding
Flu viruses employ an arsenal of tactics to bypass the immune system, and now Ivan Marazzi and colleagues at the Laboratory of Immune Cell Epigenetics and Signaling at Rockefeller University have discovered a new trick: a protein of the H3N2 flu strain carries a sequence that looks like a human histone tail and accumulates in the nuclei of infected cells, where it interferes with the transcription of antiviral genes.

The steal
The configuration of a portion of the viral protein NS1 in the human H3N2 strain looks similar enough to a region on the human histone protein that it can regulate the assembly of chromatin complexes. Crucially, the histone mimic targets antiviral host genes, and binds and impairs a protein that plays a key role in regulating transcription elongation.

The basics
“It’s been long established that viral mimicry can occur,” said cancer researcher Joe Mymryk of the University of Western Ontario, who was not involved in the study and has recently found other evidence of epigenetic manipulation by viruses. “But when you find one like this that’s just so basic and so critical, I think it’s an exciting development.”

The prognosis
By mediating our response to the flu virus, Marazzi thinks the histone-mimic proteins may be beneficial—to both human and virus. Because this mediation of the body’s response balances viral virulence with host survival, H3N2 has persisted for more than 30 years. “It looks like the sequence has been maintained through positive selection,” said Marazzi.

Rethinking Herbal Medicine

A phylogenetic study of traditional plant remedies could aid drug development.

By Beth Marie Mole | September 10, 2012

The medicinal New Zealand flax (Phormium sp.). Phormium species are used traditionally by Māori people to treat a wide range of conditions, including skin, respiratory and gastro-intestinal problems. University of Warwick, United Kingdom, Andrew Clarke

Many scientists raise a skeptical eyebrow to traditional herbal treatments, but a new phylogenetic study suggests that such remedies may hold promise—for both medicine and drug development.

In the study, researchers from the University of Reading in the United Kingdom found that many medicinal plants used by nearly 100 cultures on different continents are related. Because these distant groups of people likely identified their plant therapies independently, such herbal treatments may be legit, the researchers argue, and the plants likely contain bioactive compounds that scientist could exploit for new drug therapies.

“People think there’s nothing new to be found,” said John Beutler, a leading chemist at the National Cancer Institute’s Center for Cancer Research, who was not involved in the study. “But, that’s just not true. Wherever we look, we find new stuff.” But critics still doubt whether researchers will be able to sort effective traditional remedies from the bogus ones, and whether pharmaceutical endeavors will follow.

In previous studies that tried to use cultural comparisons to find useful remedies, scientists struggled to make meaningful taxonomic comparisons. “If [local] floras are different, obviously plants that are used in traditional medicine will be different,” said Royal Botanic Gardens Kew postdoc Haris Saslis-Lagoudakis, lead author of the study, which was published today (September 10) in the Proceedings of the National Academies of Science. But Haris and his colleagues’ phylogenetic comparisons allowed them to link seemingly unrelated plants.

They constructed genus-level phylogenetic trees of plants from 3 disparate locations—New Zealand, Nepal, and the Cape of South Africa. Once they assembled their trees, they overlaid ethnobotanical data regarding the therapeutic uses of various plants by cultures from each of the three locations (one culture from New Zealand, three cultures from The Cape of South Africa, and more than 80 cultures from Nepal).

In the flora phylogenies for each of the three continents, medicinal plants clustered into “hot nodes,” meaning they were more related to each other than the other plants in the analysis. Further, categorizing medicinal plants by what condition they treated, the researchers found that medicinal plants clustered
into condition-specific nodes, even when the analyses from all three locations were combined—again suggesting a high degree of relatedness for plants used to treat similar conditions and lending some validity to these herbal treatments.

Biomedical researchers have occasionally drawn from ethnobotany and traditional treatments when looking for new drugs, but the use of this strategy has waned in recent decades. Though more than 80 percent of plant species have not been tested for therapeutic potential, the last major drug discovered from plants was the cancer drug Taxol in 1967.

This lack of interest stems, in part, from skepticism about the legitimacy of traditional plant therapies. Many cultures use medicinal plants for multiple ailments, for example. If a plant is good for your stomach, people may start taking it for problems with their nearby liver, then their lungs, then their heart and head, and so on, said Daniel Moerman, a professor emeritus of the University of Michigan-Dearborn and a leading expert on ethnobotany and cross-cultural studies. This makes it difficult to determine what condition a medicinal plant may effectively treat.

Haris, who recently completed his PhD at the University of Reading, sidestepped the issue by accounting for all the documented conditions each plant treated. “We scored everything—all of the uses that are defined—and let the results speak for themselves.”

Another criticism facing the study is that cultures sometimes use symbolic visual cues to identify potentially disease-treating plants. For example, it may be common for traditional healers to treat menstrual symptoms with plants that have red flowers, explains evolutionary biologist and senior researcher on the study Julie Hawkins. Such appearance-based selection would suggest that relatedness of medicinal plants is due to looks, not bioactivity.

“But, we’re finding a lot of morphological variation amongst [related medicinal plants],” Hawkins said, which suggests that visual cues don’t explain their relatedness.

The researchers also looked at plants being developed or already in use as drug therapies around the globe and found a significant number fell in the nodes with the traditional medicinal plants, further supporting the validity of the method in identifying plants useful for drug discovery. The team noted several plant genera related to traditional medicinal plants that have not been tested for bioactivity, which could serve as low-hanging fruit in the search for new therapies.

Both Beutler and Moerman expressed skepticism, however, that pharmaceutical companies would jump at the new approach to guiding their drug discovery, as the industry has largely shifted toward robotic, high-throughput screens of chemical libraries. But new approaches are always welcome, Beutler said. “The perception is that we’re doing the same old grind and find, and it’s just not the case.”

**Ebola Outbreak In DRC Responsible For As Many As 31 Deaths, According To Revised Count**

"An outbreak of Ebola hemorrhagic fever has claimed possibly as many as 31 lives in the northeast of the Democratic Republic of Congo since May, Health Minister Felix Kabange Numbi said Thursday," Agence France-Presse reports. "Numbi said an international committee for technical and scientific coordination in the fight against Ebola had carried out retrospective research to find previous cases, which raised the death toll," according to the news agency (9/13). "We can expect an increase in the number of cases as more people are tracked. These are not necessarily new cases," WHO spokesperson Tarik Jasarevic said, adding, "I want to stress that this is a serious outbreak, and there is a risk of the Ebola virus spreading, but we would not say that it’s out of control," NPR’s health blog "Shots" reports (Doucleff, 9/13). "The latest WHO figures show there are now 65 probable or suspected cases of Ebola in Congo, with 108 people under surveillance," Reuters notes (9/13). "Last month an outbreak of a more deadly Ebola strain in neighboring Uganda killed 16 people, but health workers say the two outbreaks do not appear to be related," according to BBC News (9/13).

**Some Guinean Residents Seek Cholera Vaccine; Outbreak In Sierra Leone Winding Down**

With nearly 6,000 reported cholera cases, including more than 100 deaths, Guinea is facing the worst cholera outbreak since 2007, and "some residents of the capital Conakry are clamoring to be vaccinated," IRIN reports. "The cholera vaccine has shown promising results in the handful of communities where it has been used: none of those vaccinated have been infected," the news service writes, noting, "For now cholera vaccination is not generally done on a large scale." According to IRIN, "WHO and partner agencies are planning a cholera vaccine stockpile for epidemic control and looking at the possibility of
introducing the two-dose oral vaccine into national immunization programs in endemic areas," but the agency also "says such stockpiles should not detract from other prevention efforts: detection, diagnosis, and treatment of cases with oral rehydration and antibiotics; establishment of a safe water supply; implementation of adequate waste disposal, sanitation, and hygiene; and communication and social mobilization."

"Neighboring Sierra Leone is facing its worst cholera epidemic since 1995, with 15,834 cases, including 251 deaths as of 3 September, according to [the U.N. Office for the Coordination of Humanitarian Affairs (OCHA)]." IRIN reports (9/13). However, a statement from the government released on Wednesday said, "The improved partnership and cooperation between government and development partners, including other stakeholders, and the effective management of cases, has resulted in a reduction in cholera cases throughout the country." The statement notes that a National General Cleaning exercise has been scheduled for the end of September "as a means of maintaining a clean and healthy environment." In addition, "UNICEF is providing litter bins for markets in Freetown, while mobile telephone companies are currently working towards constructing more public toilets in Freetown as part of their corporate social responsibilities," the statement said (9/12).

**Floods, Cholera in Niger Have Claimed 162 Lives Since July, OCHA Reports**

"Floods in Niger have killed 81 people since July, the U.N. Office for Humanitarian Affairs [OCHA] announced Thursday, adding cholera outbreaks have killed a further 81 people," Agence France-Presse reports. "Thousands of homes, schools, health centers and mosques have been destroyed, along with large quantities of food supplies, according to the authorities," the news service writes, adding, "Cholera is spreading fast in at least four places, making 3,854 people sick and notably affecting the Tillaberi regions lying by the Niger river and close to the border with Mali, OCHA said." The news service notes, "In neighboring Burkina Faso, heavy rains have killed 18 people and made 21,000 homeless since June. ... Senegal and Nigeria have also been affected by the bad weather" (9/13).

**X-Rays Reveal the Self-Defence Mechanisms of Bacteria**

ScienceDaily (Sep. 14, 2012) — A research group at Aarhus University has gained unique insight into how bacteria control the amount of toxin in their cells. The new findings can eventually lead to the development of novel forms of treatment for bacterial infections.

Many pathogenic bacteria are able to go into a dormant state by producing persister cells that are not susceptible to conventional antibiotics. This causes serious problems in the treatment of life-threatening diseases such as tuberculosis, where the presence of persister cells often leads to a resurgence of infection following medical treatment.

At the molecular level, the formation of persister cells is due to the presence of toxins that are produced by the bacteria themselves, and which enable them to enter the dormant state. During this hibernation period, the bacteria constantly regulate the amount of toxin at exactly the same level and thus maintain the dormant state.

![Diagram](image)
In an article recently published in the American scientific journal Structure, the researchers at the Department of Molecular Biology and Genetics, Aarhus University, present new results that reveal the molecular details of the regulatory mechanism of toxins.

By isolating and crystallising the toxin molecules and their molecular companions—the antitoxins—and by subsequently exposing the crystals to strong X-rays, the research team (consisting of the two PhD students Andreas Bøggild and Nicholas Sofos and Associate Professor Ditlev E. Brodersen) gained unique insight into how bacteria control the amount of toxin in the cell.

The new findings can eventually lead to the development of entirely new forms of treatment of bacterial infections that work initially by blocking toxin function and production, and subsequently by using traditional antibiotics to fight the pathogenic bacteria.

Journal Reference:
Andreas Bøggild, Nicholas Sofos, Kasper R. Andersen, Ane Feddersen, Ashley D. Easter, Lori A. Passmore, Ditlev E. Brodersen. The Crystal Structure of the Intact E. coli RelBE Toxin-Antitoxin Complex Provides the Structural Basis for Conditional Cooperativity. Structure, 2012; DOI: 10.1016/j.str.2012.08.017

'Siloed' Agencies Hindered in Efforts to Fight Animal-To-Human Diseases, Analysis Finds
ScienceDaily (Sep. 13, 2012) — The "siloed" structure of U.S. health agencies is hindering efforts to spot and combat animal-to-human afflictions, such as West Nile Virus, New York University sociologist Colin Jerolmack has concluded after conducting an organizational analysis of their operations.

Even though many newly emerging infectious diseases readily spread from one species to another, Jerolmack found that "agency members interpret certain diseases as 'livestock diseases' or 'wildlife diseases,' and they view categories of animals outside their purview as irrelevant to their institutional prerogatives. Consequently, there is little sense of mutual understanding and common goals—and thus little coordination—across these various organizations."

Jerolmack's study, which appears in the journal Sociology of Health and Illness, examined the following agencies and departments: a state Department of Health (DOH); the Department of Agriculture (USDA); a state Department of Wildlife; a state Department of Agriculture; and the Centers for Disease Control and Prevention (CDC). Through interviews with agency or departmental personnel, he looked at how the distinct organizational cultures of these agencies produced incompatible or even competing agendas that hampered efforts to respond to zoonoses—infectious diseases that can be passed between species.

Jerolmack’s interviews revealed several instances in which agencies and departments adopted a siloed, rather than cooperative, approach when faced with zoonoses:

* A state Department of Agriculture official who bristled at efforts to remove livestock that may have posed a health risk to residents because, "We're here to support anyone doing farming [and] keeping animals... We want people to continue keeping animals on their property."
* "Strained" relationships between a state’s Department of Health and Department of Agriculture "sometimes meant that the DOH did not receive information on circulating diseases in animals that may become a problem for humans later on." A DOH employee, noting that bird flu strains, particularly those found in livestock, can mutate quickly, said such outbreaks should be considered vital public health information—a view not shared by that state’s Department of Agriculture.

- A city public health official, responding to an outbreak of salmonella, did not turn to the state’s Department of Agriculture, the USDA, or any other agencies involved in animal health for help or information. Nor did it share information with them. The official "mentioned the need to change residents' cultural practices, but neglected veterinary medicine solutions," Jerolmack recounts.
- The same agency adopted a siloed approach in addressing other zoonoses, such as Lyme disease and West Nile virus: "It did not regularly communicate with animal agencies or analyze surveillance data on disease outbreaks in animals, but instead responded with medical and educational campaigns once one or more people became infected," Jerolmack writes.

Even instances in which agency cooperation has led to medical breakthroughs—such as the discovery that West Nile Virus may be transmitted from birds to humans—has not produced reform.

"Though the discovery of West Nile was greeted with alarm and massive pesticide sprays, it did not usher in a sea change regarding zoonotic surveillance and communications across states and agencies," Jerolmack observes, adding that a USDA official told him that following the West Nile outbreak in 1999, agency and departmental practices returned to "business as usual."
Jerolmack notes the CDC has recognized the need to do a better job of building relationships with the veterinary world. In 2006, it created the Geographic Medicine and Health Promotion Branch, which tracks the flows of both humans (as travelers) and animals (as they are imported or exported), and its director, Dr. Nina Marano, is a veterinarian. He adds that during an outbreak of rabies in the 1990s, state agencies worked together to stem the tide of the disease—a response he views as an "example of the successful alignment of priorities and action among the myriad agencies responsible for human and animal health."

However, his study found these instances to be the exception rather than the norm. "Although each agency's institutionalized habits of thought and action may have been relatively well-adapted to addressing the diseases that traditionally concerned each organization," Jerolmack writes, "they constrain members from building the inter-organizational and interdisciplinary bridges required to manage the latest 'hybrid' diseases."

Journal Reference:

HIV infection doesn't generally affect the response to syphilis treatment

Michael Carter
Published: 18 September 2012
Well-controlled HIV infection does not have a significant impact on the serological response to treatment for syphilis, Swiss investigators report in the online edition of Clinical Infectious Diseases. However, they found that syphilis stage was a significant factor in the response to treatment.

"HIV coinfection did not influence the overall time to serological response to treatment," write the authors. “The clinical stage of syphilis had a significant impact on the serological response; compared with the primary stage, latent syphilis showed a slower treatment response."

The sexually transmitted infection syphilis is a global health problem. There are an estimated 12 million new cases each year, 90% of which are in developing countries. New diagnoses of syphilis are also increasing in industrialised countries, and a large number of infections involve people with HIV.

Syphilis can be treated with antibiotics. Serological monitoring is used to monitor the response to such treatment.

Studies conducted in the early years of the HIV epidemic suggested that infection with HIV led to a poorer response to syphilis treatment. However, in the era of modern antiretroviral therapy, it is uncertain if this is still the case. It is also unclear if the syphilis stage has an impact on individual responses to therapy.

Given these uncertainties, investigators in Switzerland designed a retrospective study involving 264 people. Their aims were to compare serological response to treatment between different stages of syphilis and to examine the influence of HIV infection.

The people included in the study received care between 1999 and 2008 and received treatment within two weeks of their syphilis diagnosis. For most of them, therapy consisted of one or three doses of Benzathine penicillin G. Serological follow-up was performed 20 to 375 days after therapy.

Three different methods were used to monitor serological response:

- The Veneral Disease Research Laboratory (VDRL) test.
- An IgM capture ELISA.
- The Treponemal Pallidum Particle Agglutination (TPPA) test.

Most of the people in the study (92%) were men and 42% were known to be living with HIV. The majority of people with HIV received aggressive treatment and received three doses of penicillin G.

In all, 90 people presented with primary syphilis, 133 with secondary syphilis, 33 with latent infection and eight with tertiary syphilis.

Initial VDRL and TPPA syphilis titres were significantly lower (p < 0.001) and more likely to be negative (p < 0.001) for people with primary syphilis compared to other stages of the disease.

However, 7% of people with primary syphilis with negative VDRL and TPPA tests had positive serology using the IgM test.

“We therefore suggest,” write the authors, “that in cases of suspected early infection specific IgM ELISA should be used in addition to other screening tests. It is important that clinicians communicate suspicion of an early infection to the laboratory.”

The serological response to therapy was then monitored.
VDRL analysis showed that a response (fourfold drop in titre or reversion to non-reactive) was achieved within a median of 37 days for people with primary infection, 49 days for those with secondary syphilis and 68 days for people with latent syphilis.

Three months after treatment 85 to 100% of those with primary syphilis had achieved a treatment response, as had 76 to 89% of people with secondary syphilis and between 44 and 79% of people with latent infection.

VDRL serological response was affected by syphilis stage. Compared to primary syphilis, latent infection was associated with a significantly slower treatment response (HR = 0.34; 95% CI, 0.2-0.57) and there was a trend towards a slower response for people with secondary syphilis (HR = 0.74; 95% CI, 0.53-1.05).

Infection with HIV did not have a major impact on the response to treatment. However, people living with HIV who had primary syphilis and a CD4 cell count below 500 cells/mm³ had a slower response compared to HIV-negative people who also had primary syphilis (HR = 0.37; 95% CI, 0.17-0.81; p = 0.012).

“As most of our HIV infected patients probably had a restored immune system, we would not expect to find a significant difference in regard to serological response rate,” comment the investigators.

A total of 190 people were followed for a year or until their VDRL test ceased to be reactive. Some 81% had a non-reactive test within twelve months. People who continued to have a reactive test after this point were more likely to have latent or tertiary syphilis 52 vs 9% of reactors (p < 0.001). Almost all these patients had baseline high titres. For one person, it took 4.2 years for tests to cease to be reactive.

Using the ImG test, the median time to a treatment response was 130 days for people with primary syphilis, 245 days for those with secondary infection and 202 days for people with latent syphilis. Treatment response was not influenced by HIV infection, regardless of CD4 cell count. However, both secondary and latent syphilis were associated with a slower treatment response than primary syphilis.

“Our study provides evidence that a combination of the TPPA test and an IgM ELISA is superior to the VDRL for diagnosing of syphilis,” comment the authors. “The syphilis disease stage significantly influences treatment response, whereas HIV coinfection has an impact on the response only in primary syphilis.”

Reference

Navajo Nation Reports HIV/AIDS Increases
Farmington Daily Times, New Mexico. (09.17.2012) Jenny Kane
A report from the Indian Health Service, the Navajo Nation Health Education Program, and the Navajo AIDS Network indicate that in the past 25 years HIV cases have increased in the Navajo Nation. In the mid-1990s, the number of new cases averaged 10 per year, compared to about 40 per year in the last three years. There were 35 new cases in 2010 and 40 in 2011. HIV/AIDS rates among the Navajo population increased first in homosexual males, then in heterosexual males and females, similar to the pattern of the United States, except ten years later. Other Native peoples also are reporting high rates of HIV/AIDS. The Indian Health Service website shows HIV and AIDS rates for Native Americans and Alaska Natives rank third in the United States, after those of African Americans and Hispanics. According to the Office of Minority Health, Native Americans/Alaska Natives have a 30 percent higher rate of infection than Caucasians, and men have a 50 percent higher rate. Hospitals on the Navajo Nation, including the Gallup Indian Medical Center, are focusing on HIV screening. The Navajo Nation Council passed the Navajo Nation HIV/AIDS Act in 2011 in support of research, prevention, and treatment of HIV/AIDS on the reservation. Part of the difficulty of stemming the spread of HIV/AIDS among Native Americans includes the lack of education and discussion about sex, as well as the alcoholism and illegal drug use. Information on HIV/AIDS in the Navajo Nation is available from the Navajo Nation Health Education Program, Window Rock, Arizona, at (928) 871-6258.

Prisoner in African Jail Sues to Get HIV Meds
Lawyers for an AIDS awareness campaigner in Zimbabwe are taking a landmark test case to Zimbabwe’s Supreme Court. The case concerns forcing police and prison authorities to ensure that people with HIV get their life prolonging medication. The plaintiff was arrested for being one of the bystanders at a lecture in Harare that police claimed was in preparation for a revolt in the country. He was later freed without
being charged. The plaintiff, who has been HIV-infected for 18 years, said in court papers that he was denied appropriate antiretroviral treatment in jail for three weeks in 2011, and his condition worsened. Also, he had been kept in a filthy crowded cell, held in solitary confinement for demanding his medications, and on the day of his arrest, Harare police did not allow him to call his family to bring medication he took twice a day on an exact timetable. After the lawyers intervened, his family was able to bring the medication two days later, but it was kept by the police and he was given a prison issue tablet once a day. In the court papers, he states that he is dependent on the medications and a healthy diet to stay alive. No official figures are currently available on deaths in Zimbabwe’s prisons and police cells. The lawyers claim that his plight and that of thousands of other prison inmates with medical conditions who do not get treatment is a denial of the basic constitutional right to life, especially for prisoners who have not been found guilty of any crime.

**Man Gets 30 Years in Hepatitis C Case**

*Associated Press.* (09.11.2012)

A 49-year old radiology technician in Jacksonville, Florida, was sentenced to 30 years in federal prison after pleading guilty to stealing syringes of painkillers meant for patients’ procedures. He had replaced the syringes with syringes of saline contaminated with Hepatitis C virus, which subsequently caused a patient’s death. The technician tampered with the syringes from 2006-2008, while employed at the Mayo Clinic branch in Jacksonville. A three-year investigation finally linked the hepatitis C outbreak to the technician who was then fired and reported to the police.

**Number Of Recorded Dengue Cases Up 36% Over Last Year In Costa Rica**

"A total of 8,480 people have been affected by dengue fever in Costa Rica" so far this year, representing an increase of 36 percent, or 2,230 more cases than during the same period last year, according to a Ministry of Health report, Xinhua News reports. "Among all the cases so far, only nine people were affected by hemorrhagic dengue fever, which is a more serious and sometimes mortal type of dengue, the report added," the news service writes (9/17). Health authorities are urging people to eliminate possible sources of reproduction for mosquitoes, including disposing of old tires, according to a health ministry press release (9/11).

**Viruses not to blame for chronic fatigue syndrome after all**

Contrary to previous findings, new research finds no link between chronic fatigue syndrome and the viruses XMRV (xenotropic murine leukemia virus-related virus) and pMLV (polytropic murine leukemia virus). A study to be published on September 18 in *mBio*, the online open-access journal of the American Society for Microbiology, reveals that research that reported patients with chronic fatigue syndrome carried these two viruses was wrong and that there is still no evidence for an infectious cause behind chronic fatigue syndrome.

"The bottom line is we found no evidence of infection with XMRV and pMLV. These results refute any correlation between these agents and disease," says Ian Lipkin of Columbia University, a co-author on the study.

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME), is a disabling condition in which sufferers experience persistent and unexplained fatigue as well as any of a host of associated problems, including muscle weakness, pain, impaired memory, and disordered sleep. Medical treatment for CFS/ME costs as much as $7 billion every year in the U.S. alone.

The possible causes of CFS/ME have been argued and researched for years with no success. Results from separate studies in 2009 and 2010 that reported finding retroviruses in the blood of patients with CFS/ME created a sensation among patients and the medical community and offered hope that a tractable cause for this disease had finally been found. Since then, other investigators have been unable to replicate the results of those studies, casting doubt on the idea that these viruses, XMRV and pMLV, could be behind CFS/ME.

Lipkin says the National Institutes of Health wanted conclusive answers about the possible link. "We went ahead and set up a study to test this thing once and for all and determine whether we could find footprints of these viruses in people with chronic fatigue syndrome or in healthy controls," says Lipkin. The study in *mBio* puts the speculation to rest, he says. Scientists were wrong about a potential link between chronic fatigue syndrome and these viruses.
The study authors recruited almost 300 people, 147 patients with CFS/ME and 146 people without the syndrome, to participate. Researchers tested blood drawn from these subjects for the presence of genes specific to the viruses XMRV and pMLV, much in the way the earlier studies had done. But in this study, researchers took extraordinary care to eliminate contamination in the enzyme mixtures and chemicals used for testing, which may have been the source of viruses and genes detected in the earlier studies. XMRV and pMLV are commonly found in mice but there has never been a confirmed case of human infection with these viruses.

The authors of this study include many of the authors of the original papers that reported finding XMRV and pMLV in the blood of CFS/ME patients. This is an important point, says Lipkin, as their participation should lend credibility to the pre-eminence of these newer results over the flawed earlier studies, which offered a certain amount of false hope to the CFS/ME community.

Research on the causes of CFS/ME will continue, says Lipkin. "We've tested the XMRV/pMLV hypothesis and found it wanting," he says. But, he says, "we are not abandoning the patients. We are not abandoning the science. The controversy brought a new focus that will drive efforts to understand CFS/ME and lead to improvements in diagnosis, prevention and treatment of this syndrome."

No. 26/September 18, 2012

New Findings on Protein Misfolding

Misfolded proteins can cause various neurodegenerative diseases such as spinocerebellar ataxias (SCAs) or Huntington’s disease, which are characterized by a progressive loss of neurons in the brain. Researchers of the Max Delbrück Center for Molecular Medicine (MDC) Berlin-Buch, Germany, together with their colleagues of the Université Paris Diderot, Paris, France, have now identified 21 proteins that specifically bind to a protein called ataxin-1. Twelve of these proteins enhance the misfolding of ataxin-1 and thus promote the formation of harmful protein aggregate structures, whereas nine of them prevent the misfolding (PLoS Genetics, doi: 10.1371/journal.pgen.1002897)*.

Now, Dr. Spyros Petrakis, Dr. Miguel Andrade, Professor Erich Wanker and colleagues have identified 21 proteins that mainly interact with ataxin-1 and influence its folding or misfolding. Twelve of these proteins enhance the toxicity of ataxin-1 for the nerve cells, whereas nine of the identified proteins reduce its toxicity.

Furthermore, the researchers detected a common feature in the structure of those proteins that enhances toxicity and aggregation. It is a special structure scientists call "coiled-coil-domain" because it resembles a double twisted spiral or helix. Apparently this structure promotes aggregation, because proteins that interact with ataxin-1 and have this domain enhance the toxic effect of mutated ataxin-1. As the researchers said, this structure could be a potential target for therapy: “A careful analysis of the molecular details could help to discover drugs that suppress toxic processes.”

Identification of Human Proteins That Modify Misfolding and Proteotoxicity of Pathogenic Ataxin-1; Spyros Petrakis1, Tamás Raskó1, Jenny Russ1, Ralf P. Friedrich1, Martin Stroedicke1, Sean-Patrick Riechers1, Katja Muehlenberg1, Angeli Möller1, Anita Reinhardt1, Arunachalam Vinayagam1, Martin H. Schaefer1, Patrick Riechers1, Michael Boutros1, Hervé Tricoir1, Miguel A. Andrade-Navarro1, Erich E. Wanker1

International Medical Corps Responding to Hepatitis E Outbreak in South Sudan


The International Medical Corps (IMC) rolled out an Outbreak Preparedness and Response Strategy for Hepatitis-E Virus (HEV) in response to an outbreak that occurred in Maban County, South Sudan. HEV causes an infection of the liver and can be transmitted by ingesting water and food contaminated with feces. HEV usually proliferates in places with inadequate hygiene. So far, 31 cases of HEV have been confirmed throughout refugee camps in Maban, and 16 deaths have been recorded, with the number of cases increasing daily. IMC’s outbreak strategy includes active surveillance, treatment, management, and referral protocol. The organization is also creating a 24-hour, 10-bed isolation unit to manage hemorrhagic jaundice cases. Community outreach, social mobilization, and active surveillance of acute
jaundice cases are in progress. To raise awareness, the IMC carried out a series of community leader trainings, concentrating on signs and symptoms of HEV; methods of preventing HEV; and the importance of timely referral, particularly for pregnant females. IMC has trained 25 community volunteers on health and hygiene promotion, health education, and active case finding of acute jaundice. Also, the IMC is providing primary health care, nutrition, water, and hygiene and sanitation services in the Gendrassa refugee camp. For more information, visit: http://internationalmedicalcorps.org/page.aspx?pid=2374.

**Bishop Stands Firm Against STD Vaccine in Catholic Schools Despite Lawsuit Threat**


A lobby group, HPV Calgary, has threatened a lawsuit against Calgary's Roman Catholic school district, because it refuses to participate in a program for administering the human papillomavirus (HPV) vaccine in its schools. The vaccine prevents certain strains of the disease that can lead to cervical cancer. The Roman Catholic school district has instead directed parents to clinics where the children can get the vaccination. Bishop Fred Henry, the Bishop of Calgary, commented that administering the vaccine would undermine the schools' effort to teach children about abstinence and chastity in accord with the teachings of the Catholic church. The Calgary Catholic school district is now Canada's only school board in a major city that does not offer the vaccine. It has been banned by Catholic school boards in eight other districts of Alberta, as well as in Yellowknife and Halton, Ontario.

**WHO Working With Partners To Stop Ebola From Spreading In DRC**

The WHO on Tuesday "said it is continuing to work with authorities from the Democratic Republic of the Congo (DRC) to stop an Ebola outbreak from spreading, with the number of detected cases having reached 46 in the past week," the U.N. News Centre reports. Of the detected cases, 19 have been fatal, and 26 other cases have been identified and are being investigated, according to the WHO, the news service notes. "In a news release, WHO said it is working with the Global Outbreak Alert and Response Network to provide support by deploying experts to the field to work with partners," and "the country's ministry of health is working on an epidemiological investigation to identify all possible chains of transmission of the illness and ensure that appropriate measures are taken to interrupt the transmission, and stop the outbreak," the news service writes (9/18).

NPR's "Shots" blog reports on the challenges health care workers face in treating Ebola patients and stopping the spread of the virus. The blog also notes "50 leading experts on Ebola and similar deadly viruses are gathering Wednesday and Thursday at the National Institutes of Health outside Washington to assess several promising treatments for these diseases" (Knox, 9/19).

**WHO Increasing Efforts To Fight Cholera In Sierra Leone**

An ongoing cholera outbreak continues to affect Sierra Leone, and the WHO said on Tuesday it is increasing efforts to fight the disease, "as fatalities from the water and food-borne disease continue to increase," the U.N. News Centre reports. "In a press statement, the [WHO] confirmed that the total number of reported cases had reached 18,508, including 271 deaths, since the beginning of 2012, with the highest cluster of infections occurring in the western area of the country where the capital, Freetown, is located," the news service writes, noting the agency is working with the government and other partners "to step up their response" (9/18).

**Researchers identify possible key to slow progression toward AIDS**

One of the big mysteries of AIDS is why some HIV-positive people take more than a decade to progress to full-blown AIDS, if they progress at all.

Although the average time between HIV infection and AIDS in the absence of antiretroviral treatment is about 10 years, some individuals succumb within two years, while so-called slow progressors can stay healthy for 20 years or longer.

Researchers already know that many slow progressors carry a gene called HLA-B*57 (B57), an immune gene variant that is found in less than 5 percent of the general population but in 40 to 85 percent of slow progressors. Yet even among those with the B57 gene, the speed of disease progression can vary considerably.

Now, a group of investigators from the Multi-Center AIDS Cohort Study (MACS), housed within the UCLA AIDS Institute, may have uncovered the key to this variation. It is a killer T-cell immune response that occurs early on in HIV infection and targets a section — or epitope — of the HIV protein called IW9.
The novel findings are featured on the cover of the October issue of the Journal of Virology. "Since the hope for a vaccine is that it would elicit immune control, the thought has been that understanding how B57 protection works would yield helpful lessons and principles for vaccine design," said Catherine Brennan, an assistant research scientist in the department of medicine at the David Geffen School of Medicine at UCLA and the study's lead author. "There have been a lot of efforts to understand how the immune response to HIV in B57 carriers is superior to the response in non-B57 carriers, but it has been hard to nail anything down conclusively."

HLA-B genes are known to work by activating killer T cells that recognize unique sections of proteins, or epitopes, but it has been a mystery which section or sections of HIV protein HLA-B57 and the killer T cells work through.

Previous research had largely focused on the killer T-cell response after several years of infection. However, Beth D. Jamieson, a professor of medicine at the Geffen School of Medicine and the study's principal investigator, believes that the most critical responses are likely to occur early during infection, when the T cells are still strong and can reduce the number of places where HIV hides out in the human body.

Researchers have studied the immune response in the early months of infection, but since it is not easy to predict at early stages which people will ultimately become slow progressors, correlating early immune responses with long-term outcomes has been difficult.

"What made this kind of study possible for us is the Multicenter AIDS Cohort Study, which is an incredible longitudinal study," Brennan said.

The MACS has been freezing blood samples every six months since 1984 from thousands of men either at risk of HIV infection or already infected. "The size and duration of the study, along with the careful documentation of participant health and stewardship of frozen samples, allowed us to recover blood samples taken shortly after HIV infection from 14 HLA-B57 carriers with known infection dates and known long-term outcomes," Brennan said. "This allowed us to correlate early immune responses with long-term outcomes."

It was important to the researchers to compare only the killer T-cell responses among those with the B57 gene variant, instead of comparing the responses of those with and without B57. Although B57 carriers have, on average, much better prognoses than non-carriers, there is tremendous variability among the population, and not all do well, Jamieson said.

"Since possession of the B57 variant is not sufficient, we wanted to determine what specific immune events in B57 carriers are associated with immune control of the virus," she said. "We found that those who targeted the IW9 epitope early in infection had significantly longer times until onset of AIDS than those who did not. The finding that targeting of IW9 seems to be important is novel, as this epitope had been overlooked in many earlier studies of B57 and HIV."

The researchers cautioned that the study was based on a small sample of only 14 individuals and that a wider pool of subjects is needed to replicate their findings. Also, their results point to a correlation with — not causation of — slower disease progression among B57 carriers who target the IW9 epitope soon after HIV infection. "This work, although not powered by a large cohort and necessarily exploratory in nature, does suggest that the role of IW9 targeting in B57-mediated protection merits closer attention," the researchers conclude. "Understanding the detailed mechanisms by which B57 is associated with slow progression to disease will reveal underlying principles of immune control of HIV-1, which is critical for the development of rational vaccine-design strategies."

**Genome Digest**

What researchers are learning as they sequence, map, and decode species’ genomes

By Beth Marie Mole | September 18, 2012
**Globe trotting parasite**
Species: *Plasmodium vivax*
Genome size: ~27 million base pairs

Interesting fact: The malaria parasite, *Plasmodium vivax*, can share alleles across the globe, according to researchers at Case Western Reserve University and the Cleveland Clinic Lerner Research Institute. The researchers sequenced isolates of the parasite from Madagascar, Cambodia, El Salvador, and a monkey-adapted strain from South America, and found evidence for a high amount of gene sharing, raising concern that the parasites could rapidly spread drug resistance genes around the world. The parasites are such good travelers because they can lie dormant in a patient’s liver for months and reemerge in a new locale.


**Rabid virus**
Species: *Ikoma lyssavirus*
Genome size: 12 thousand base pairs

Interesting fact: Lyssaviruses, single-strand negative-sense RNA viruses, cause rabies in animals and humans around the world. Vaccines are highly effective at protecting against the common deadly virus, but little is known about viral variation that might undermine vaccine protection. Researchers from the Wildlife Zoonosis & Vector-Borne Diseases Research Group in Surrey, United Kingdom, sequenced the most genetically distinct rabies virus yet, found in a rabid African civet in Tanzania. The new genomic information could help researchers stay one step ahead of the virus.


**UGANDA: Condom use infrequent despite rising HIV rates**

No glove, no love

KAMPALA, 21 September 2012 (PlusNews) — Despite nationwide efforts to increase HIV awareness and common fears of unplanned pregnancy, young, sexually active Ugandans continue to have risky sex without using condoms consistently, spurring new measures to promote the prophylactic.

Only 36.2 percent of women and 52.9 percent of men between 20 and 24 used a condom during their last sexual intercourse in the past 12 months, according to the National AIDS Indicator Survey, launched on 18 September. Among those who had more than two partners in the past 12 months, only 23.4 percent of women and 30 percent of men reported using a condom during their last intercourse. The research also reveals that a majority of young Ugandans lack comprehensive knowledge about HIV; just 39 percent of men and women aged 15 to 24 have all the facts on how HIV is spread and how it can be prevented.

The country’s HIV prevention strategies have been called into question following a rise in HIV prevalence from 6.4 percent to 7.3 percent over the past five years.

Uganda has long relied on the ‘ABC-plus' model, which includes abstinence, being faithful and condom use, as well as measures to prevent the mother-to-child-transmission of HIV and, more recently, methods such as medical male circumcision. Government officials say there is a need for more focus on condom use for young people.

"The students should go for protected sex... It's the only way to reduce HIV prevalence rates in the country," David Kihumuro Apuuli, director general of the Uganda AIDS Commission, told IRIN/PlusNews.

Greater fear of pregnancy

Some students at Kampala’s Makerere University seem more concerned about pregnancy than about contracting sexually transmitted infections. Even so, many do not use condoms.

"Of course I trust my boyfriend, [but] I fear getting pregnant because my parents will refuse to pay my tuitions fees," Sharon Nalule, a Makerere student, told IRIN/PlusNews. "We would rather continue using morning after pills."
Pharmacies around Makerere do a brisk trade in "morning after" pills every weekend. "We normally sell those drugs throughout the week, however, the sales are higher over the weekend," said Lorna, a nurse at a pharmacy near the university. "It's when students have more time to drink, party and enjoy... they go for it [sex]—some without protection."

Emergency contraceptive pills retail for about US$4, compared to condoms, which cost between $0.25 and $2 for a pack of three. But for many young couples, condom use stops after a certain comfort level is reached within a relationship.

"I have always had unprotected sex with my girlfriend after an HIV/AIDS test. I trust her. However, I fear her getting pregnant. So at times I advise her to get morning after pills," Peter Okello, a second-year student at Makerere University, said.

Emergency contraceptive pills contain high doses of hormones that disrupt the normal menstrual cycle and can be taken up to five days after unprotected sex to prevent pregnancy. They are not intended for regular use, and taking them frequently may cause the menstrual cycle to become irregular.

There is no formal education about the morning after pill in Uganda, which most girls learn about from their friends. "The youths at university are at their prime stage. They are very inquisitive... They engage in drugs and alcoholism, and indulge in unprotected sex, which sometimes leads to contracting HIV/AIDS, sexually transmitted infections and unwanted pregnancies," said Alex Craig Kiwanuka, youth project officer at the NGO Reproductive Health Uganda (RHU).

**Condom campaign**

When the current semester at Makerere started in August, RHU launched an HIV prevention campaign that includes the distribution of free condoms and other contraceptives by students to their peers at Makerere University and the Mulago Paramedical School. The students also distribute T-shirts, stickers and flyers with accurate information about the proper use of the morning after pill.

"We were trained and equipped. We don't just give the condoms and contraceptives. We first teach and demonstrate to... [the students] how to use them. Many of the students lack correct information," James Bukenya, a peer educator, told IRIN/PlusNews. "Extending these services to where students are staying increases... utilization of... condoms and contraceptives." The campaign aims to ensure that students engage in "satisfying, pleasurable and risk-free sexual intercourse".

"This is a pilot project targeting at least 5,000 students this year. Depending on its success and availability of funds... we may be able to roll it out to all institutions of higher learning in the country," said RHU’s Kiwanuka. "Our team will educate, counsel and refer their colleagues for testing, safe male circumcision and treatment at health facilities."

Angel Nakimbugwe, a social sciences student and peer educator, told IRIN/PlusNews, "The campaign should be extended to other institutions of higher learning. There are many students who lack information and need these services."

**UCLA Researchers Gain Insight into Why HIV Progression Differs Among Individuals**

Examiner.com, (09.19.2012) Robin Wulffson, MD

Researchers at the University of California, Los Angeles, have discovered why some HIV positive individuals progress more rapidly than others to full-blown AIDS. The research was published in the Journal of Virology. Slow progressors carry the gene called HLA-B*57 (B57) an immune gene variant found in less than five percent of the population, but in 40-85 percent of slow progressors. Among those with the B57 gene, the speed of disease progression also varies. The key to the variation is a killer T-cell immune response occurring early in the HIV infection. It targets a section or epitope of the HIV protein known as IW9. The researchers compared only the killer T-cell responses among those with the B57 gene, using blood taken shortly after HIV infection from 14 HLA-B57 carriers with known infection dates and known long-term outcomes. It was found that those whose killer T-cell immune response targeted the IW9 epitope early in the infection had significantly longer times until onset of AIDS than those who did not. The researchers note that the study sample was small—14 subjects—and that the study should be repeated with a larger number of subjects. Also, the results point to a correlation with, rather than causation of slower disease progression among B57 carriers who target the IW9 epitope soon after infection.

The full report was published in the Journal of Virology (October 2012; 86:10505-10516).
Medical College of Wisconsin Study Finds Awareness of New Jersey HIV Exposure Law is Not Associated with Reduced Sexual Risk Behavior

Rachel Mosey

Researchers at the Medical College of Wisconsin (MCW) surveyed HIV-infected persons in New Jersey between March 22, 2010 and October 6, 2010 on the New Jersey law that requires HIV-positive individuals to disclose their status to sexual partners. Carol Galletly, JD and PhD, of the Center for AIDS Intervention Research at MCW and the principal investigator of the study together with her colleagues found that the law does not seem to be an effective deterrent that prevents HIV transmission. Although 51 percent of study participants reported knowledge of the law, those who knew and those who did not were just as likely to reveal their status, engage in less risky sexual behaviors, and use condoms. Most of the participants, whether aware of the law or not, reported complying with the law for the previous year. Eighty-five percent of the participants stated that they were not willing to have unprotected sex with a seronegative partner who was unaware of their HIV-positive status.

Knowledge of the law was not associated with negative outcomes for HIV-infected study participants. Persons aware of the law did not report greater social hostility toward persons with HIV or experience more discomfort with HIV-status disclosure or more HIV-related stigma. On the other hand, those who were not aware of the law perceived more social hostility toward HIV-infected persons, experienced greater HIV-related stigma, and were less comfortable with HIV-status disclosure.

The 479 study participants, who were aged 19 to 66 years, were 45 percent female and were approximately 66 percent African American, 16 percent Hispanic, and 13 percent Caucasian. When the researchers questioned them about responsibility for HIV prevention, 90 percent believed that an HIV-infected person bore at least half of the responsibility for ensuring that their seronegative partners did not contract the disease through sex, and 54 percent felt the HIV-infected person had the full responsibility. The article, “New Jersey's HIV Exposure Law and the HIV-Related Attitudes, Beliefs, and Sexual and Seropositive Status Disclosure Behaviors of a Sample of Persons Living with HIV,” was published ahead of print in the American Journal of Public Health (doi: 10.2105/AJPH.2012.300664)

Study examines delayed, misdiagnosis of sporadic Jakob-Creutzfeldt disease

CHICAGO – A medical record review study of 97 patients with the fatal, degenerative brain disorder sporadic Jakob-Creutzfeldt disease (sCJD) suggests that a correct diagnosis of the disease was often delayed by a variety of misdiagnoses, according to a report published Online First by Archives of Neurology, a JAMA Network publication.

The disease is often misdiagnosed because of a variability of early symptoms and signs, a variability in disease duration and a lack of recognition of the condition in the medical community. Often, sCJD is mistaken for other neurodegenerative conditions such as Alzheimer disease and dementia with Lewy bodies, according to the study background.

Ross W. Paterson, M.R.C.P., and colleagues from the University of California, San Francisco, retrospectively reviewed all cases referred to the UCSF Memory and Aging Center rapidly progressing dementia and CJD clinical research program between August 2001 and February 2007. They identified 97 patients with pathology-proven sCJD for whom they had sufficient medical records (40 women and 57 men who ranged in age from 26 to 83 years).

The 97 patients had received a combined total of 373 alternative diagnoses prior to their diagnosis of likely CJD, with an average of 3.8 misdiagnoses per patient. The physicians who most commonly made the misdiagnoses were primary care physicians and neurologists. In the 18 percent of patients (17 patients) who were correctly diagnosed at their first assessment, the diagnosis was almost always made by a neurologist. The average time from onset to diagnosis was almost eight months, an average of two-thirds the way through the disease course, according to the study results.

"In any patient with a rapidly progressive dementia who has been given multiple potential diagnoses, sCJD must be considered," the authors comment.

Researchers note that "early and accurate" diagnosis of sCJD is valuable for public health reasons and to allow for potential treatments to be tested as early as possible in the disease course.

"It would therefore be valuable to improve early and accurate diagnosis of sCJD premortem to identify at-risk persons, allowing for public health measures that would prevent transmission to healthy individuals through blood donation, infected surgical equipment and or other medical procedures," the authors conclude.

AIDS patients face risk for esophageal, stomach cancers

People with AIDS are at increased risk for developing esophageal and stomach carcinoma as well as non-Hodgkin lymphomas (NHLs), according to a new study in *Gastroenterology*, the official journal of the American Gastroenterological Association.

"People diagnosed with AIDS are living longer due to improved therapies. However, they remain at increased risk of developing a number of different cancers," said E. Christina Persson, PhD, of the National Cancer Institute and lead author of this study. "An elevated risk of esophageal and stomach cancers had been observed before, but we were able to look at risk for subtypes of these malignancies."

In this study, researchers analyzed data from the HIV/AIDS Cancer Match Study, which links data collected from 1980 to 2007 for 16 U.S. population-based HIV and AIDS and cancer registries. They compared risks of stomach and esophageal cancers in 596,955 people with AIDS with those of the general population.

Those with AIDS had a 69 percent and 44 percent increased risk of esophageal and stomach carcinomas, respectively. The risks of NHLs — tumors of immune cells — in the stomach and esophagus were also strongly elevated. Additionally, the researchers' analysis showed a significant 53 percent increased risk of cancer of the lower stomach in people with AIDS. Since *Helicobacter pylori* infection is one of the causes of this type of stomach cancer, one explanation for an increased risk of this cancer might be an increased prevalence of *H. pylori* in people with AIDS.

Another explanation for this elevated cancer risk could be more frequent use of tobacco and alcohol among people with AIDS. Programs encouraging tobacco cessation and alcohol moderation may help reduce the occurrence of esophageal and stomach carcinomas among these patients.

Eye proteins have germ-killing power, could lead to new antimicrobial drugs, study finds

By Sarah Yang, Media Relations | September 24, 2012

BERKELEY —

When it comes to germ-busting power, the eyes have it, according to a discovery by UC Berkeley researchers that could lead to new, inexpensive antimicrobial drugs.

A team of UC Berkeley vision scientists has found that small fragments of keratin protein in the eye play a key role in warding off pathogens. The researchers also put synthetic versions of these keratin fragments to the test against an array of nasty pathogens. These synthetic molecules effectively zapped bacteria that can lead to flesh-eating disease and strep throat (*Streptococcus pyogenes*), diarrhea (*Escherichia coli*), staph infections (*Staphylococcus aureus*) and cystic fibrosis lung infections (*Pseudomonas aeruginosa*).

The findings, to be published in the October issue of the *Journal of Clinical Investigation*, could lead to a powerful new weapon in the battle against disease-causing invaders. These keratin fragments are relatively easy to manufacture, making them good candidates for low-cost therapeutics, the study authors said.

“What’s really exciting is that the keratins in our study are already in the body, so we know that they are not toxic, and that they are biocompatible,” said the study's principal investigator, Suzanne Fleiszig, a professor at UC Berkeley’s School of Optometry who specializes in infectious diseases and microbiology. “The problem with small, naturally occurring, antimicrobial molecules identified in previous research is that they were either toxic or easily inactivated by concentrations of salt that are normally found in our bodies.”

These new small proteins in the study were derived from cytokeratin 6A, one of the filament proteins that connect to form a mesh throughout the cytoplasm of epithelial cells.

“We used to think that cytokeratins were primarily structural proteins, but our study shows that these fragments of keratin also have microbes-fighting capabilities,” said study lead author Connie Tam, an assistant research scientist in Fleiszig’s lab. “Cytokeratin 6A can be found in the epithelial cells of the human cornea as well as in skin, hair and nails. These are all areas of the body that are constantly exposed to microbes, so it makes sense that they would be part of the body’s defense.”

In a commentary published alongside the study, Michael Zasloff, professor of surgery and pediatrics at Georgetown University’s School of Medicine, said these “keratin-derived antimicrobial peptides appear to be exciting new biocompatible candidates for development as human anti-infective therapeutics.”
The researchers in Fleiszig’s lab came upon cytokeratin 6A in their efforts to solve the mystery behind the eye’s remarkable resilience to infection. They noticed that the surface of the eye, unlike other surfaces of the body, did not have bacteria living on it, and that corneal tissue could handily wipe out a barrage of pathogens in lab culture experiments.

“It is very difficult to infect the cornea of a healthy eye,” said Fleiszig. “We’ve even used tissue paper to damage the eye’s surface cells and then plastered them with bacteria, and still had trouble getting bacteria to enter the cornea. So we proposed that maybe there were antimicrobial factors that are unique to the eye.”

In the hunt for this mystery compound, the researchers cultured human corneal epithelial cells and exposed them to the *P. aeruginosa* bacteria. They used mass spectrometry to sort out which peptides were most active in fighting off the bacteria. Cytokeratin 6A-derived peptides emerged the winners, and surprisingly, peptide fragments as short as 10 amino acids were effective.

To confirm that they got the right protein, the researchers used gene-silencing techniques to reduce the expression of cytokeratin 6A in the cornea of mice. With a key defense disabled, the amount of bacteria that adhered to the corneas increased fivefold.

Tests showed that cytokeratin 6A-derived fragments could quickly kill bacteria in water and in a saline solution, showing that the salt contained in human tears would not dilute the protein’s effectiveness. Other experiments indicated that cytokeratin 6A fragments prevented the bacteria from attacking epithelial cells, and that the proteins cause bacterial membranes to leak, killing the pathogen within minutes.

The researchers noted that further research could reveal numerous different keratin fragments in the body’s innate defense system.

“Keratins may represent a novel class of antimicrobials with the potential to be designed to selectively kill specific pathogens,” said Tam.

**Large Bacterial Population Colonized Land 2.75 Billion Years Ago**

ScienceDaily (Sep. 24, 2012) — There is evidence that some microbial life had migrated from Earth’s oceans to land by 2.75 billion years ago, though many scientists believe such land-based life was limited because the ozone layer that shields against ultraviolet radiation did not form until hundreds of millions years later.

But new research from the University of Washington suggests that early microbes might have been widespread on land, producing oxygen and weathering pyrite, an iron sulfide mineral, which released sulfur and molybdenum into the oceans.

"This shows that life didn't just exist in a few little places on land. It was important on a global scale because it was enhancing the flow of sulfate from land into the ocean," said Eva Stüeken, a UW doctoral student in Earth and space sciences.

In turn, the influx of sulfur probably enhanced the spread of life in the oceans, said Stüeken, who is the lead author of a paper presenting the research published Sunday (Sept. 23) in *Nature Geoscience*. The work also will be part of her doctoral dissertation.

Sulfur could have been released into sea water by other processes, including volcanic activity. But evidence that molybdenum was being released at the same time suggests that both substances were being liberated as bacteria slowly disintegrated continental rocks, she said.

If that is the case, it likely means the land-based microbes were producing oxygen well in advance of what geologists refer to as the "Great Oxidation Event" about 2.4 billion years ago that initiated the oxygen-rich atmosphere that fostered life as we know it.

In fact, the added sulfur might have allowed marine microbes to consume methane, which could have set the stage for atmospheric oxygenation. Before that occurred, it is likely large amounts of oxygen were destroyed by reacting with methane that rose from the ocean into the air.

"It supports the theory that oxygen was being produced for several hundred million years before the Great Oxidation Event. It just took time for it to reach higher concentrations in the atmosphere," Stüeken said.

The research examined data on sulfur levels in 1,194 samples from marine sediment formations dating from before the Cambrian period began about 542 million years ago. The processes by which sulfur can be added or removed are understood well enough to detect biological contributions, the researchers said.
The data came from numerous research projects during the last several decades, but in most cases those observations were just a small part of much larger studies. In an effort to provide consistent interpretation, Stüeken combed the research record for data that came from similar types of sedimentary rock and similar environments.

"The data has been out there for a long time, but people have ignored it because it is hard to interpret when it is not part of a large database," she said.

**Viruses Help Scientists Battle Pathogenic Bacteria and Improve Water Supply**

ScienceDaily (Sep. 24, 2012) — Infectious bacteria received a taste of their own medicine from University of Missouri researchers who used viruses to infect and kill colonies of *Pseudomonas aeruginosa*, common disease-causing bacteria. The viruses, known as bacteriophages, could be used to efficiently sanitize water treatment facilities and may aid in the fight against deadly antibiotic-resistant bacteria.

"Our experiment was the first to use bacteriophages in conjunction with chlorine to destroy biofilms, which are layers of bacteria growing on a solid surface," said Zhiqiang Hu, associate professor of civil and environmental engineering in MU’s College of Engineering. "The advantage to using viruses is that they can selectively kill harmful bacteria. Beneficial bacteria, such as those used to break down wastes in water treatment plants, are largely unaffected. Hence, viruses could be used to get rid of pathogenic bacteria in water filters that would otherwise have to be replaced. They could save taxpayers' money by reducing the cost of cleaning water."

Bacteria can be difficult to kill when they form a biofilm. The outer crust of bacteria in these biofilms can be killed by chlorine, but the inner bacteria are sheltered. Viruses solve this problem because they spread through an entire colony of bacteria. Hu noted that the bacteriophages are easier to create than the enzymes used to attack biofilms. The viruses also are better at targeting specific bacterial species.

Hu, along with MU’s recent graduate, Yanyan Zhang, found the greatest success in killing biofilms by using a combination of bacteriophages and chlorine. An initial treatment with viruses followed by chlorine knocked out 97 percent of biofilms within five days of exposure. When used alone, viruses removed 89 percent of biofilms, while chlorine removed only 40 percent.

"The methods we used to kill *Pseudomonas aeruginosa* could be used against other dangerous bacteria, even those that have developed resistance to antibiotics," said Hu. "Our work opened the door to a new strategy for combating the dangers and costs of bacterial biofilms. The next step is to expand our experiment into a pilot study."

**Journal Reference:**

**Late start for ART in pregnancy increases HIV transmission risk during breastfeeding period**

Carole Leach-Lemens
Published: 27 September 2012

A high viral load at the time of starting treatment during pregnancy and a shorter time on antiretroviral therapy (ART) before delivery continued to place mothers at risk of passing on HIV during the breastfeeding period for at least seven months after giving birth, researchers report in a sub-study of the Kisumu Breastfeeding Study in Kenya, published in the advance online edition of the *Journal of Acquired Immune Deficiency Syndromes*.

Among this cohort of 434 women, over 80% had an adherence rate equal to or greater than 95%. Twenty-four infants were infected with HIV during the seven-month study period with over 50% infected during delivery. Eleven of the mothers of infected infants had a viral load over 10,000 copies/ml. Viral load was linked to vertical (mother-to-child) transmission at delivery (p = 0.0028), at 14 weeks (p = 0.05) and at 24 weeks after delivery (p = 0.01).

These findings lend further support to the World Health Organization’s (WHO) guidelines of starting ART prophylaxis early, for the greatest reduction in maternal viral load, for the prevention of mother-to-child transmission (PMTCT). HIV continues to be one of the leading causes of death in sub-Saharan Africa, where over half of those infected are women of reproductive age. ART has had a considerable effect on reducing death and disease among people with HIV.

Women in sub-Saharan Africa are often diagnosed during pregnancy and depending on eligibility criteria (CD4 cell counts) start ART for their own health or to prevent vertical transmission. For those
women not eligible for treatment for their own health, ART throughout breastfeeding is recommended for infant protection.

CD4 cell counts and clinical staging, while imperfect, are used to determine eligibility and treatment response in resource-poor settings where viral load monitoring is often unavailable. CD4 cell counts alone often do not have the sensitivity to detect rising viral load until treatment failure and HIV progression is apparent.

Good adherence is critical to improve health outcomes, delaying viral resistance as well as preventing transmission to the baby.

Since a high viral load is a risk factor for transmission, the goal of ART is to reduce viral load to undetectable levels. So the mother’s health will determine the health and survival of the infant.

With this in mind, the authors chose to evaluate immunologic response, viral load suppression and adherence among women getting ART prophylaxis consisting of lamivudine/zidovudine and either nevirapine or nelfinavir in the Kisumu Breastfeeding Study. They also looked at other risk factors that affected time to viral load suppression.

The Kisumu Breastfeeding Study, an open-label clinical trial, enrolled women between July 2003 and November 2007 to look at the efficacy of, tolerance and adherence to maternal triple ART for PMTCT up to 24 weeks after delivery.

Women were enrolled into this sub-study if they had adherence, viral load and CD4 data in at least three time points during the study period: from 32 to 34 weeks of pregnancy to 24 weeks after delivery.

Among the 434 women remaining in the sub-study baseline demographic data, trends in CD4 cell count and viral load at enrolment, delivery, 14 and 24 weeks after delivery were analysed. Pill counts in addition to self-report and drug calendar determined adherence rates. Adherence was defined as equal to or above 95%.

Significant improvements in virological response and immunological status provided solid support for triple ART for PMTCT in resource-poor settings.

Women with undetectable viral load at baseline increased from 6 to 79%; women with CD4 cell counts under 250 cells/mm$^3$ decreased from 100 (23%) at baseline to 22 (5%) at 24 weeks after delivery.

Most women (84%) were adherent throughout the study period.

There were no significant differences in the proportion of women who achieved undetectable viral load at 24 weeks after delivery based on CD4 cell count categories.

However, the authors note their findings showed the importance of timing of maternal ART for PMTCT. The longer the women were on treatment before delivery the greater the chance of undetectable viral load: 35%, 54%, 71% and 81% of the women on ART for under two weeks, 2-4 weeks, 4-6 weeks and over six weeks, respectively, before delivery achieved undetectable viral load.

Since the intervention began in the third trimester, it is not surprising that a longer time on ART increased the possibility of undetectable viral load at delivery, they add.

More women achieved an undetectable viral load on a nelfinavir-based ART regimen compared to a nevirapine-based ART regimen and in a shorter time frame. At delivery 58% (130/226) of women on a nevirapine-based ART regimen compared to 82% (139/170) of women on a nelfinavir-based ART regimen achieved undetectable viral load.

The difference between the two regimens remained after controlling for baseline CD4 cell counts, baseline viral load and time on treatment (OR=2.02, 95% CI: 1.16-3.54, p=0.014).

While adherence is linked to viral suppression, the authors note that in a subset of women with CD4 cell counts above 250 cells/mm$^3$ there was no correlation between adherence and viral suppression. So the authors question how much adherence is needed for viral suppression and how accurate are the measures used for assessing adherence? Or perhaps, they add, some women achieved undetectable viral load between tests and then rebound within the same interval.

While close to 70% had increased CD4 cell counts equal to or above 500 cells/mm$^3$ at 14 weeks the proportion did not change at 24 weeks. This would suggest, note the authors, an immunological response to ART can be assessed as soon as 14 weeks after starting treatment.

The original study was designed to look at nevirapine-based ART for PMTCT and was later modified to include nelfinavir-based ART in some women. So the finding that nelfinavir-based ART improved virologic response is, the authors point out, an unplanned secondary analysis and the results considered preliminary.

This study shows viral load remains a risk factor for MTCT. The findings suggest, the authors note, possibly more women would have achieved undetectable viral load by delivery had they started ART earlier. As such these have important implications for PMTCT during pregnancy and delivery.
The authors conclude “to ensure long term success of PMTCT which involves extended use of ART, we must identify feasible and reliable tools to assess adherence and provide real-time interventions to support optimal adherence among these HIV-infected women.”

Reference

**Consistent and correct condom use reduces risk of bacterial STIs by 60%**

Michael Carter
Published: 26 September 2012

Consistent and correct condom use provides a high level of protection against bacterial sexually transmitted infections (STIs), US investigators report in *Sexually Transmitted Infections*. Individuals who always used condoms correctly were almost 60% less likely to be diagnosed with an infection. Consistent condom use on its own did not reduce the risk of bacterial STIs.

“Efforts to promote condom use should be augmented with efforts to promote their correct use,” write the authors. “Condom use errors and problems are a global issue. Incomplete use of condoms is a problem requiring targeted education. Rectifying issues such as poor fit and feel of condoms and using oil-based lubricants may substantially reduce slippage and breakage.”

Condoms are a cornerstone of HIV prevention and sexual health campaigns. A number of well-designed studies have shown their protective effect against male-to-female transmission of herpes, chlamydia, gonorrhoea, syphilis and human papillomavirus (HPV).

However, whether condoms provide protection against the acquisition of STIs remains controversial. Research looking at this question has had number of important limitations. The most important of these is a failure to adjust for incorrect use of condoms (not using condoms from the start to the finish of penetrative sex) or condom ‘accidents’ such as slippage and breakage.

“Failure to control for condom breakage and slippage may produce the analytical equivalent of condom non-use,” observe the investigators. “A prospective study of clinic attendees found 13% incidence of chlamydia and gonorrhoea among people reporting consistent condom use but also reporting at least one problem with incorrect use. In contrast, among those reporting consistency and lack of problems...no incident infections were found.”

Previous research has also relied on study participants accurately remembering whether they used condoms and if they encountered problems. Investigators in the US therefore designed a prospective study involving attendees at five sexual health clinics. Participants received daily prompts to electronically recall incidents of penile-vaginal sex and use of condoms.

The investigators wanted to see if consistent condom use was protective against three common bacterial STIs: chlamydia, gonorrhoea and trichomonas. They also wished to determine the protective effect associated with consistent and correct use of condoms.

A total of 929 people were recruited to the study. A urine sample was taken at the start of the study to screen for STIs and further samples were submitted for testing after three and six months of follow-up. Most of the study participants were women (55%) and African American (65%). Their mean age was 29 years and the mean number of reported lifetime sexual partners was 30.

Participants reported a total of 14,970 penile-vaginal sex events, 64% of which involved the use of a condom. Approximately a quarter of sex events (24%) with a condom involved an error or problem.

A total of 118 STIs were diagnosed during follow-up. Incidence of STIs was 8.46% among those reporting less than consistent condom use. This compared to an incidence of 6.71% in people who reported using condoms all the time. This difference was not statistically significant.

The incidence of infections among people who reported less than consistent use of condoms and incorrect use of condoms or problems with slippage or breakage was 8.75%. The incidence among individuals who reported consistent and correct condom use was significantly lower at 3.35% (p = 0.023).

“Participants who used condoms both correctly and consistently were estimated to have 59% smaller odds of acquiring an STI over 3 months compared to participants who did not use condoms both correctly and consistently,” note the authors. “Magnified over an entire population, this level of risk reduction for sexually active people is substantial.”
They believe that their findings probably underestimate the protective effect of condom use against bacterial STIs: "The six incident cases observed for people using condoms consistently and correctly may be a result of an unprotected sex event, breakage event, etc that was not reported...tendencies to forget, fabricate, exaggerate and under-report are inevitable."

Reference

**U.N. Presents Plan To Improve Access To Contraception, Releases Report On Maternal, Child Health**
The U.N. on Wednesday "presented a plan to make life-saving health supplies more accessible, while a new report found that, despite impressive reductions in maternal and child mortality in the past decade in some countries, millions of women and children still die every year from preventable causes," the [U.N. News Centre](http://www.un.org) reports. "With its new plan, the U.N. Commission on Life-Saving Commodities for Women and Children aims to improve access and use of essential medicines, medical devices and health supplies that effectively address causes of death during pregnancy, childbirth and into childhood," the news service writes (9/26). "Prices for long-acting contraception will be halved for 27 million women in the developing world through [the] new partnership, former President Bill Clinton and other world leaders announced" on the sidelines of the U.N. General Assembly, the [Associated Press](http://www.ap.org) writes. "The deal will help avoid almost 30 million unwanted pregnancies and save an estimated $250 million in health costs, the partnership said," according to the AP (DePasquale, 9/26).

"The plan comes as the Secretary-General's independent Expert Review Group on Information and Accountability for Women's and Children's Health issued its first report, concluding that while reductions in maternal and child mortality during the past decade have been impressive in some countries, millions of women and children still die every year from preventable causes," the U.N. News Centre notes (9/26). "Declining donor funding is one of the reasons most of the world will not meet the United Nations' Millennium Development Goals for women's and children's health by 2015, according to" the report, [HealthDay News/U.S. News & World Report](http://www.healthday.com) writes (9/26). "The report's authors said governments, donors, non-governmental organizations, health professionals, researchers, foundations and the private sector can all play an important role in improving child and maternal health," and made several recommendations, [CBS News](http://www.cbsnews.com) adds (9/26).

**Large Donors Dictating Direction Of Global Health Research, Financing, Essay Says**
"When it comes to getting aid right, an all-too-familiar problem seems to be balancing the priorities of rich governments with what communities actually want," [AlertNet](http://www.alertnet.org) reports in an article examining an essay written by Oxford University researcher Devi Sridhar and published in [PLOS Medicine](http://www.plosmedicine.org). The essay "assesses the system of financing for health research," according to the news service (Nguyen, 9/26).

"Sridhar argues that since the priorities of funding bodies largely dictate what health issues and diseases are studied, a major challenge in the governance of global health research funding is agenda-setting, which in turn is a consequence of a larger phenomenon—'multi-bi financing.,'" according to a PLOS [press release](http://www.plos.org) (9/25). "Multi-bi financing refers to the practice of donors choosing to route non-core funding—earmarked for specific sectors, themes, countries, or regions—through multilateral agencies such as the World Health Organization (WHO) and the World Bank and to the emergence of new multi-stakeholder initiatives such as the Global Fund to Fight AIDS, Tuberculosis and Malaria and the GAVI Alliance," she writes.

Sridhar examines the driving forces behind new patterns of global health funding and governance, and discusses three possible consequences of multi-bi financing for global health research governance (9/25). "Sridhar argues that the risk of multi-bi financing is that difficult choices about priority-setting in health will be made in the marketplace of global initiatives, rather than in the community that will have to live with those choices," the press release states. She writes, "The shift to multi-bi financing likely reflects a desire by participating governments, and others, to control international agencies more tightly," according to the press release. However, she adds that "one major impact of multi-bi financing has been to shine a clear light on how and where multilateral institutions, such as the World Bank and the World Health Organization, might do better," the press release notes (9/25).
Obama's U.N. Speech Could Be 'Turning Point' In Fight Against Human Trafficking

"When President Obama made a landmark speech against modern slavery on Tuesday, many of us in the news media shrugged," but women survivors of human trafficking "noticed," Nicholas Kristof writes in his New York Times column. "[T]he world often scour[s] the victims and sees them as criminals: these girls are the lepers of the 21st century," he says, adding, "So bravo to the president for giving a major speech on human trafficking and, crucially, for promising greater resources to fight pimps and support those who escape the streets. Until recently, the Obama White House hasn't shown strong leadership on human trafficking, but this could be a breakthrough. The test will be whether Obama continues to press the issue."

Kristof notes that girls and women who are trafficked are at a greater risk of contracting HIV or other diseases and becoming victims of rape and violence. "Prostituted kids are among the most voiceless of the voiceless around the world, and it will make a difference if the White House speaks up for them—and fights for them," he writes, adding, "So let's demand that police officers and prosecutors go after pimps and johns, while treating the teenagers as victims who need comprehensive social services." He concludes, "[L]et's make sure that this isn't just a speech, but a turning point" (9/27).

New way of fighting high cholesterol upends assumptions

Atherosclerosis – the hardening of arteries that is a primary cause of cardiovascular disease and death – has long been presumed to be the fateful consequence of complicated interactions between overabundant cholesterol and resulting inflammation in the heart and blood vessels.

However, researchers at the University of California, San Diego School of Medicine, with colleagues at institutions across the country, say the relationship is not exactly what it appears, and that a precursor to cholesterol actually suppresses inflammatory response genes. This precursor molecule could provide a new target for drugs designed to treat atherosclerosis, which kills tens of thousands of Americans annually.

The findings are published in the September 28, 2012 issue of Cell.

Lurking within our arterial walls are immune system cells called macrophages (Greek for "big eater") whose essential function is to consume other cells or matter identified as foreign or dangerous. "When they do that, it means they consume the other cell's store of cholesterol," said Christopher Glass, MD, PhD, a professor in the Departments of Medicine and Cellular and Molecular Medicine and senior author of the Cell study. "As a result, they've developed very effective ways to metabolize the excess cholesterol and get rid of it."

But some macrophages fail to properly dispose of the excess cholesterol, allowing it to instead accumulate inside them as foamy lipid (fat) droplets, which gives the cells their particular name: macrophage foam cells.

These foam macrophages produce molecules that summon other immune cells and release molecules, signaling certain genes to launch an inflammatory response. Glass said conventional wisdom has long assumed atherosclerotic lesions – clumps of fat-laden foam cells massed within arterial walls – were the
unhealthy consequence of an escalating association between unregulated cholesterol accumulation and inflammation.

Glass and colleagues wanted to know exactly how cholesterol accumulation led to inflammation, and why the macrophages failed to do their job. Using specialized mouse models that produced abundant macrophage foam cells, they made two unexpected discoveries that upend previous assumptions about how lesions form and how atherosclerosis might be more effectively treated.

"The first is that foam cell formation suppressed activation of genes that promote inflammation. That's exactly the opposite of what we thought happened," said Glass. "Second, we identified a molecule that helps normal macrophages manage cholesterol balance. When it's in abundance, it turns on cellular pathways to get rid of cholesterol and turns off pathways for producing more cholesterol."

That molecule is desmosterol – the final precursor in the production of cholesterol, which cells make and use as a structural component of their membranes. In atherosclerotic lesions, Glass said the normal function of desmosterol appears to be "crippled."

"That's the next thing to study; why that happens," Glass said, hypothesizing that the cause may be linked to overwhelming, pro-inflammatory signals coming from proteins called Toll-like receptors on macrophages and other cells that, like macrophages, are critical elements of the immune system.

The identification of desmosterol's ability to reduce macrophage cholesterol presents researchers and drug developers with a potential new target for reducing the risk of atherosclerosis.

Glass noted that a synthetic molecule similar to desmosterol already exists, offering an immediate test-case for new studies. In addition, scientists in the 1950s developed a drug called triparanol that inhibited cholesterol production, effectively boosting desmosterol levels. The drug was sold as a heart disease medication, but later discovered to cause severe side effects, including blindness from an unusual form of cataracts. It was pulled from the market and abandoned.

"We've learned a lot in 50 years," said Glass. "Maybe there's a way now to create a new drug that mimics the cholesterol inhibition without the side effects."

September 27, 2012

**Sandia probability maps help sniff out food contamination**

Tracking down the source of fresh food contamination can be difficult and time-consuming. Uncovering the sources of fresh food contamination could become faster and easier thanks to analysis done at Sandia National Laboratories’ National Infrastructure Simulation and Analysis Center (NISAC).

The study, in the *International Journal of Critical Infrastructures*, demonstrates how developing a probability map of the food supply network using stochastic network representation might shorten the time it takes to track down contaminated food sources. Stochastic mapping shows what is known about how product flows through the distribution supply chain and provides a means to express all the uncertainties in potential supplier-customer relationships that persist due to incomplete information.

If used on a larger scale, such methods also might assess the vulnerability of food supplies to wide-scale, deliberate contamination.

Tracking down the source of fresh food contamination can be difficult and time-consuming. Sandia analyst Stephen Conrad said difficulties in adequately characterizing connections and product flows among producers, distributors and suppliers can contribute to significant uncertainty in assessing the risk of foodborne illness.

“This is often a serious problem when there is an outbreak of food poisoning in a particular region and the healthcare authorities cannot quickly trace the source of the outbreak,” Conrad said.

When an outbreak occurs, epidemiologists must interview affected people to track down where foodborne exposures happened. Often those interviews take place weeks after the exposure, leading to inaccurate or incomplete information and making it difficult to pinpoint a likely food culprit. Once the tainted food has been identified, investigators must trace up through the food distribution supply chain to locate the source of contamination.

“Epidemiologists involved in trace back start behind the eight ball,” Conrad said. “They attempt to reconstruct the pathway the contaminated food has traveled through the distribution network well after the fact.”

Even at the supply chain level, investigating how food moves through the system is daunting. Conrad said supply chains vary widely from one food marketing system and agricultural sector to another. Some supply chain parts change frequently. Even within a single agricultural sector, some parts may be
characterized by enduring supplier/customer relationships, while others may be market-based and highly transitory.

Even industry insiders may not understand the supply chain map. Many only know “one up and one down” — that is, they know only their direct supplier and direct customer. Some information about customers and suppliers can be proprietary and therefore hard to get, Conrad said.

**Stochastic food chain mapping could prevent more healthy food from being lost to outbreak concerns.**

In 2011, sprouts were the focus of a serious E. coli outbreak in Europe, but tracing contaminated products to their source proved difficult.

Sandia researchers applied the stochastic mapping technique to test data from the fresh sprout sector in a single state in the U.S., using a case study of the edible seed sprout distribution system as the basis of their computational model.

“Stochastic network representation provides the ability to incorporate and express the uncertainties using probability maps,” Conrad explained. “The method enables effective risk analysis and designing robust food defense strategies.”

Future work for the team will include scaling the analysis up to the company or industry level as well as mapping commodity flows into, out of and within a geographic region.

Ultimately, NISAC intends to work with partners in business and federal and state agencies to ascertain whether the agencies have a business case for adopting the method. If there is, the team will seek to help achieve wide acceptance of using data analysis to assess risk.

Building on techniques and knowledge developed at NISAC over the past four years, the work was initiated with funding from Sandia’s Laboratory Directed Research and Development program and continued with funding from the Department of Homeland Security.

“If stochastic mapping was widely used now, perhaps outbreaks, such as the recent ones involving salmonella, could be more quickly tracked down and contained. Quicker containment would benefit not only consumers but also the farmers who grow fresh food for our nation and who can be severely impacted economically by uncertainties and market restrictions on sales of their products caused by delays in pinpointing an outbreak’s source,” Conrad said.


**Popular HIV Drug May Cause Memory Declines**

ScienceDaily (Sep. 27, 2012) — The way the body metabolizes a commonly prescribed anti-retroviral drug that is used long term by patients infected with HIV may contribute to cognitive impairment by damaging nerve cells, a new Johns Hopkins research suggests.

Nearly 50 percent of people infected with HIV will eventually develop some form of brain damage that, while mild, can affect the ability to drive, work or participate in many daily activities. It has long been assumed that the disease was causing the damage, but Hopkins researchers say the drug efavirenz may play a key role.

People infected with HIV typically take a cocktail of medications to suppress the virus, and many will take the drugs for decades. Efavirenz is known to be very good at controlling the virus and is one of the few that crosses the blood-brain barrier and can target potential reservoirs of virus in the brain. Doctors have long believed that it might be possible to alleviate cognitive impairment associated with HIV by getting more drugs into the brain, but researchers say more caution is needed because there may be long-term effects of these drugs on the brain.

"People with HIV infections can't stop taking anti-retroviral drugs. We know what happens then and it's not good," says Norman J. Haughey, Ph.D., an associate professor of neurology at the Johns Hopkins University School of Medicine. "But we need to be very careful about the types of anti-retrovirals we prescribe, and take a closer look at their long-term effects. Drug toxicities could be a major contributing factor to cognitive impairment in patients with HIV."

For the study led by Haughey and described online in the Journal of Pharmacology and Experimental Therapeutics, researchers obtained samples of blood and cerebrospinal fluid from HIV-infected subjects enrolled in the NorthEastern AIDS Dementia study who were taking efavirenz.
Researchers looked for levels of the drug and its various metabolites, which are substances created when efavirenz is broken down by the liver. Performing experiments on neurons cultured in the lab, the investigators examined the effects of 8-hydroxyefavirenz and other metabolites and found major structural changes when using low levels of 8-hydroxyefavirenz, including the loss of the important spines of the cells.

Haughey and his colleagues found that 8-hydroxyefavirenz is 10 times more toxic to brain cells than the drug itself and, even in low concentrations, causes damage to the dendritic spines of neurons. The dendritic spine is the information processing point of a neuron, where synapses—the structures that allow communication among brain cells—are located.

In the case of efavirenz, a minor modification in the drug's structure may be able block its toxic effects but not alter its ability to suppress the virus. Namandje N. Bumpus, Ph.D., one of the study's other authors, has found a way to modify the drug to prevent it from metabolizing into 8-hydroxyefavirenz while maintaining its effectiveness as a tool to suppress the HIV virus.

"Finding and stating a problem is one thing, but it's another to be able to say we have found this problem and here is an easy fix," Haughey says.

Haughey says studies like his serve as a reminder that while people infected with HIV are living longer than they were 20 years ago, there are significant problems associated with the drugs used to treat the infection.

"Some people do seem to have this attitude that HIV is no longer a death sentence," he says. "But even with anti-retroviral treatments, people infected with HIV have shortened lifespans and the chance of cognitive decline is high. It's nothing you should treat lightly."

**Journal Reference:**
L. B. Tovar-y-Romo, N. N. Bumpus, D. Pomerantz, L. B. Avery, N. Sacktor, J. C. McArthur, N. J. Haughey. **Dendritic spine injury induced by the 8-hydroxy metabolite of Efavirenz.** *Journal of Pharmacology and Experimental Therapeutics*, 2012; DOI: [10.1124/jpet.112.195701](http://doi.org/10.1124/jpet.112.195701)

---

**Antibiotics Could Replace Surgery for Appendicitis, Research Suggests**
ScienceDaily (Sep. 26, 2012) — Although the standard approach to acute appendicitis is to remove the appendix, a study at the Sahlgrenska Academy, University of Gothenburg, Sweden, reveals that treatment with antibiotics can be just as effective in many cases.

In her thesis, Jeanette Hansson discusses two major clinical studies of adult patients with acute appendicitis. In the first study she compares surgery with antibiotic therapy, while in the second patients with appendicitis were treated with antibiotics as first-line therapy.

Carried out at Sahlgrensa University Hospital and Kungälv Hospital, the studies showed that treatment with antibiotics was just as effective as surgery for the majority of patients.

"Some patients are so ill that the operation is absolutely necessary, but 80 percent of those who can be treated with antibiotics recover and return to full health," says Jeanette Hansson.

The thesis also shows that patients who are treated with antibiotics are at risk of fewer complications than those who undergo surgery.

The risk of recurrence within 12 months of treatment with antibiotics is around 10-15 percent.

Jeanette Hansson and her colleagues hope to be able to document the risk of recurrence over the long term and also to study whether recurrences can also be treated with antibiotics.

Even though increased resistance to antibiotics could also affect the treatment, the conclusion is that antibiotics are a viable alternative to surgery in adult patients as things stand, provided that the patient accepts the risk of recurrence.

"It's important to note that our studies show that patients who need surgery because of recurrences, or because the antibiotics haven't worked, are not at risk of any additional complications relative to those operated on in the first place," says Jeanette Hansson.

The thesis: "Antibiotic therapy as single treatment of acute appendicitis" was publicly defended in May.
Biologists at UC San Diego have unraveled the anti-viral mechanism of a human gene that may explain why some people infected with HIV have much higher amounts of virus in their bloodstream than others.

Their findings, detailed in a paper in this week’s advance online issue of the journal Nature, could also shed light on the mystery of why some people with HIV never develop symptoms of AIDS. The biologists found that a gene called Human Schlafen 11 produces a protein that inhibits the replication of HIV in infected human cells by blocking the ability of the host cell to synthesize viral proteins.

“Some people with HIV develop AIDS rapidly and others can be HIV positive for decades and never really develop any symptoms of the disease,” said Michael David, a professor of biology at UC San Diego, who headed the research team. “It's still unclear why that is, but one possibility is that the genetic variations in this protein, like in many other viral restriction factors, account for the differences in the susceptibility to the virus.”

Because Human Schlafen 11 specifically blocks synthesis of HIV proteins, the researchers are conducting further studies to see if variations in the Human Schlafen 11 gene can be correlated with disease progression in HIV infected individuals. If that turns out to be the case, the discovery could one day lead to the development of a diagnostic test for HIV infected individuals that would inform them of their likelihood of developing AIDS or, better yet, the development of a therapeutic drug that would prevent HIV infected individuals from ever developing AIDS.

“If it’s possible for the human cell to inhibit the synthesis of viral programs without affecting the synthesis of cellular proteins, it’s possible that at some point a drug can do that, too,” said David. “But our discovery is just the tip of the iceberg. There’s a lot more work to be done. Whether this will have diagnostic or therapeutic value remains to be seen.”

Human Schlafen 11 is member of a family of six genes in humans and nine genes in mice that are induced in mammalian cells in response to various kinds of infection, specifically infections that result in the release of anti-viral proteins called interferons. The first Schlafen gene was discovered in mice in 1998 by Steve Hedrick, a professor of biology.

David said his laboratory had spent the past eight years trying to figure out what role Human Schlafen 11 plays in human cells before discovering its unique role. He added that they were intrigued when Manqing Li, a project scientist in the lab, discovered that the Human Schlafen 11 protein was missing in a cell line used to produce large amounts of virus in the laboratory. “When we put Schlafen 11 back into the cell line, we got over 90 percent inhibition of virus output,” David said, confirming that the gene was critical to inhibiting virus replication.

David said that while Schlafen genes have been known for many years, his laboratory's discovery is the first to shed light on how they work at the molecular level. His team is now collaborating with several groups to determine if other Human Schlafen genes have an anti-viral effect against other viruses, such as those that cause influenza and dengue fever.

The researchers are also collaborating with scientists who oversee tissue banks containing DNA samples from thousands of individuals infected with HIV to determine whether variations in the genetic sequences of the Human Schlafen 11 gene can be correlated with the development of clinical symptoms in
those individuals. David’s team is part of a collaboration called HIV Immune Networks Team or HINT (http://hint.org/), which is funded by NIAID at the National Institutes of Health to “use systems biology approaches to reveal how the early immune response defends against HIV-1 infection with a view toward blocking virus.”

**Journal Reference:**

**How do we stop hospitals from killing us?**
If there is even a minor airplane crash in the U.S., it makes the headlines. There is a thorough federal investigation, and the tragedy often yields important lessons for the aviation industry. Pilots and airlines thus learn how to do their jobs more safely.

The world of American medicine is far deadlier: Medical mistakes kill enough people each week to fill four jumbo jets. But these mistakes go largely unnoticed by the world at large, and the medical community rarely learns from them. The same preventable mistakes are made over and over again, and patients are left in the dark about which hospitals have significantly better (or worse) safety records than their peers.

As doctors, we swear to do no harm. But on the job we soon absorb another unspoken rule: to overlook the mistakes of our colleagues. The problem is vast. U.S. surgeons operate on the wrong body part as often as 40 times a week. Roughly a quarter of all hospitalized patients will be harmed by a medical error of some kind. If medical errors were a disease, they would be the sixth leading cause of death in America—just behind accidents and ahead of Alzheimer’s. The human toll aside, medical errors cost the U.S. health-care system tens of billions a year. Some 20% to 30% of all medications, tests and procedures are unnecessary, according to research done by medical specialists, surveying their own fields. What other industry misses the mark this often?

It does not have to be this way. A new generation of doctors and patients is trying to achieve greater transparency in the health-care system, and new technology makes it more achievable than ever before.

I encountered the disturbing closed-door culture of American medicine on my very first day as a student at one of Harvard Medical School’s prestigious affiliated teaching hospitals. Wearing a new white medical coat that was still creased from its packaging, I walked the halls marveling at the portraits of doctors past and present. On rounds that day, members of my resident team repeatedly referred to one well-known surgeon as “Dr. Hodad.” I hadn’t heard of a surgeon by that name. Finally, I inquired.

“Hodad,” it turned out, was a nickname. A fellow student whispered: “It stands for Hands of Death and Destruction.”

Stunned, I soon saw just how scary the works of his hands were. His operating skills were hasty and slipshod, and his patients frequently suffered complications. This was a man who simply should not have been allowed to touch patients. But his bedside manner was impeccable (in fact, I try to emulate it to this day). He was charming. Celebrities requested him for operations. His patients worshiped him. When faced with excessive surgery time and extended hospitalizations, they just chalked up their misfortunes to fate.

Dr. Hodad’s popularity was no aberration. As I rotated through other hospitals during my training, I learned that many hospitals have a “Dr. Hodad” somewhere on staff (sometimes more than one). In a business where reputation is everything, doctors who call out other doctors can be targeted. I’ve seen whistleblowing doctors suddenly assigned to more emergency calls, given fewer resources or simply badmouthed and discredited in retaliation. For me, I knew the ramifications if I sounded the alarm over Dr. Hodad: I’d be called into the hospital chairman’s office, a dread scenario if I ever wanted a job. So, as a rookie, I kept my mouth shut. Like the other trainees, I just told myself that my 120-hour weeks were about surviving to become a surgeon one day, not about fixing medicine’s culture.

Hospitals as a whole also tend to escape accountability, with excessive complication rates even at institutions that the public trusts as top-notch. Very few hospitals publish statistics on their performance, so how do patients pick one? As an informal exercise throughout my career, I’ve asked patients how they decided to come to the hospital where I was working (Georgetown, Johns Hopkins, D.C. General Hospital, Harvard and others). Among their answers: “Because you’re close to home”; “You guys treated my dad when he died”; “I figured it must be good because you have a helicopter.” You wouldn’t believe the number of patients who have told me that the deciding factor for them was parking.
There is no reason for patients to remain in the dark like this. Change can start with five relatively simple—but crucial—reforms.

**Online Dashboards**
Every hospital should have an online informational “dashboard” that includes its rates for infection, readmission (what we call “bounce back”), surgical complications and “never event” errors (mistakes that should never occur, like leaving a surgical sponge inside a patient). The dashboard should also list the hospital’s annual volume for each type of surgery that it performs (including the percentage done in a minimally invasive way) and patient satisfaction scores.

A survey of New Yorkers found that approximately 60% look up a restaurant’s “performance ratings” before going there. If you won’t sit down for a meal before checking Zagat’s or Yelp, why shouldn’t you be able to do the same thing when your life is at stake?

Nothing makes hospitals shape up more quickly than this kind of public reporting. In 1989, the first year that New York’s hospitals were required to report heart-surgery death rates, the death rate by hospital ranged from 1% to 18%—a huge gap. Consumers were finally armed with useful data. They could ask: “Why have a coronary artery bypass graft operation at a place where you have a 1-in-6 chance of dying compared with a hospital with a 1-in-100 chance of dying?”

Instantly, New York heart hospitals with high mortality rates scrambled to improve; death rates declined by 83% in six years. Management at these hospitals finally asked staff what they had to do to make care safer. At some hospitals, the surgeons said they needed anesthesiologists who specialized in heart surgery; at others, nurse practitioners were brought in. At one hospital, the staff reported that a particular surgeon simply wasn’t fit to be operating. His mortality rate was so high that it was skewing the hospital’s average. Administrators ordered him to stop doing heart surgery. Goodbye, Dr. Hodad.

**Safety Culture Scores**
Imagine that a surgeon is about to make an incision to remove fluid from a patient’s right lung. Suddenly, a nurse breaks the silence. “Wait. Are we doing the right or the left chest? Because it says here left, but that looks like the right side.” The surgery was, indeed, supposed to be on the left lung, but an intern had prepped the wrong side. I was that doctor, and that nurse saved us all from making a terrible error. It isn’t every hospital where that nurse would have felt confident speaking up—but it’s this sort of cultural factor that is so important to safety.

If anyone knows whether a hospital is safe, it’s the people who work there. So my colleagues and I at Johns Hopkins, led by J. Bryan Sexton, administered an anonymous survey of doctors, nurses, technicians and other employees at 60 U.S. hospitals. We found that at one-third of them, most employees believed the teamwork was bad. These aren’t hospitals where you or I want to receive care or see our family members receive care. At other hospitals, by contrast, an impressive 99% of the staff reported good teamwork.

These results correlated strongly with infection rates and patient outcomes. Good teamwork meant safer care. The public needs to have access to such information for every hospital in America.

**Cameras**
It may come as a surprise to patients, but doctors aren’t very good at complying with well-established best practices in their fields. One New England Journal of Medicine study found that only half of all care follows evidence-based guidelines when applicable. Fortunately, there is a technology that could work wonders to improve compliance: cameras.

Cameras are already being used in health care, but usually no video is made. Reviewing tapes of cardiac catheterizations, arthroscopic surgery and other procedures could be used for peer-based quality improvement. Video would also serve as a more substantive record for future doctors. The notes in a patient’s chart are often short, and they can’t capture a procedure the way a video can.

Doug Rex of Indiana University—one of the most respected gastroenterologists in the world—decided to use video recording to check the thoroughness of colonoscopies being performed by doctors in his practice. A thorough colonoscopy requires meticulous scrutiny of every nook and cranney of the colon. Doctors tend to rush through them; as a result, many cancers and precancerous polyps are missed and manifest years later—at later stages.

Without telling his partners, Dr. Rex began reviewing videotapes of their procedures, measuring the time and assigning a quality score. After assessing 100 procedures, he announced to his partners that he would be timing and scoring the videos of their future procedures (even though he had already been doing this). Overnight, things changed radically. The average length of the procedures increased by 50%, and the quality scores by 30%. The doctors performed better when they knew someone was checking their work.
The same sort of intervention has been used for hand washing. A few years ago, Long Island’s North Shore University Hospital had a dismal compliance rate with hand washing—under 10%. After installing cameras at hand-washing stations, compliance rose to over 90% and stayed there.

Following Dr. Rex’s camera study, he did a follow-up, asking patients if they would like a copy of their procedure video. An overwhelming 81% said yes, and 64% were willing to pay for it. Patients are hungry for transparency.

Open Notes
Sue, a young accountant, came to my office complaining of abdominal pain. She wasn’t sure what was causing it. She offered various theories: “Could this be from my Bikram yoga?” “Did my late-night ice cream cause the pain?” “Does having unprotected sex have anything to do with it?” Throughout her visit, I took notes. When we were done, she looked down at them suspiciously.

“What did you write about me?” she asked.

She was concerned that I thought she was either nuts or an ice-cream addict. In the course of our conversation, I also learned that she wasn’t quite sure why I was recommending an ultrasound, though I thought I had told her.

I decided to start dictating my notes with the patient listening in at the end of his or her visit. “I also have high blood pressure,” was a correction one older patient blurted out. Another said, “My prior surgery was actually on the right, not the left side.” Another patient interrupted me and said, “No, I said I take 20 milligrams, not 25 milligrams, of Lipitor.” Being able to review your doctor’s notes in writing might be even better than my method, particularly if you could add your own comments, perhaps via the Web.

Harvard doctor-researchers Jan Walker and Tom Delbanco are using “open notes” at Harvard and Beth Israel Hospital in Boston, and my hometown hospital, Geisinger Medical Center in Pennsylvania, has begun giving patients online access to their doctors’ notes. So far, both patients and doctors love it.

No More Gagging
Though there are many signs that health care is moving toward increased transparency, there is also some movement backward. Increasingly, patients checking in to see doctors are being asked to sign a gag order, promising never to say anything negative about their physician online or elsewhere. In addition, if you are the victim of a medical mistake, hospital lawyers will make never speaking publicly about your injury a condition of any settlement.

We need more open dialogue about medical mistakes, not less. It wouldn’t be going too far to suggest that these types of gag orders should be banned by law. They are utterly contrary to a patient’s right to know and to the concept of learning from our errors.

Political partisans can debate the role of government in fixing health care, but for either public or private approaches to work, transparency is the crucial prerequisite. To make transparency effective, government must play a role in making fair and accurate reports available to the public. In doing so, it will unleash the power of the free market as patients are better able to take charge of their own care. When hospitals have to compete on measures of safety, all of them will improve how they serve their patients.

Transparency can also help to restore the public’s trust. Many Americans feel that medicine has become an increasingly secretive, even arrogant, industry. With more transparency—and the accountability that it brings—we can address the cost crisis, deliver safer care and improve how we are seen by the communities we serve. To do no harm going forward, we must be able to learn from the harm we have already done.

DNA with a Twist
Researchers show that DNA supercoils are dynamic structures that can “hop” long distances, a phenomenon that could affect gene regulation.

By Sabrina Richards | September 13, 2012

Scientists’ understanding of how long strings of DNA are packaged into tiny spaces just got a little more complicated. New research on single molecules of DNA show that supercoils—segments of extra-twisted loops of DNA—can move by “jumping” along a DNA strand. The results, published today (September 13) in Science, give researchers new insights into DNA organization and point to a surprisingly speedy mechanism of gene regulation inside cells.

“This is the first study that addresses the dynamics of DNA supercoils,” said Ralf Seidel, who studies movement of molecular motor proteins along DNA at the University of Technology Dresden, but was not involved in the research. This supercoil hopping motion “allows DNA strands to transmit supercoiling, bringing sites together in very fast manner.”
DNA, being a double helix, is naturally twisted. In vivo, it’s packaged with proteins called histones that help condense the millions or billions of nucleotides into the small space of a cell’s nucleus. Constant interaction with proteins moving along the strand, like transcription factors that need to open the helix to read the DNA sequence, can affect both the double helix’s twist, and the strand’s “writhe”—the coiling of the strand around itself. These extra-twisted coils, called plectonemes or supercoils, form not unlike coils in phone cords. By bringing together distant segments of DNA, such as regulatory elements and the genes they control, supercoiling can affect expression.

In order to get a better sense of how supercoils behave, Cees Dekker at Delft University of Technology and his colleagues induced supercoils in single strands of DNA molecules, labeled with fluorescent dye. One end of the DNA was anchored to the side of a glass capillary tube and a magnetic bead was attached to the other end. This allowed the researchers to use miniscule magnets to twist the DNA and induce supercoils, and watch their movement using fluorescence microscopy.

Unexpectedly, the team found that supercoils move along DNA strands in one of two ways. Sometimes they slowly diffuse along the strand; other times, the supercoils “hopped”—disappearing suddenly from one location while simultaneously appearing at a distant location further down the strand.

“This is far more complicated” than diffusion of supercoils down the DNA’s length, said Prashant Purohit, who studies DNA behavior at the University of Pennsylvania, but was not involved in the study. The DNA is behaving non-locally, he noted. “It shows that writhe”—the coiling of the DNA strand—“is a global, not local quantity [of the strand].”

So far the intriguing phenomenon has only been observed on single strands of naked DNA, Seidel cautioned, so it’s unclear how supercoils might act in vivo, when the DNA is well-packaged and studded with proteins. It may be that such behavior is more important for DNA in prokaryotic cells, which have less packaged DNA than eukaryotic cells, noted Bryan Daniels, who models biological systems at the Wisconsin Institutes for Discovery at the University of Wisconsin–Madison.

The ionic environment of the cell is also likely to influence supercoiling behavior. DNA is more likely to condense in the presence of multivalent ions (3 or more positive charges), for example, than in an environment of singly-valent ions. And Dekker and his colleagues, who used singly-valent ions in their experiments, found that more supercoils formed at lower concentrations of ions.

Dekker and his team are now looking at how different DNA sequences and the presence of DNA-binding proteins can influence supercoil formation and motion—the first step toward understanding supercoil movement in vivo.

“It’s amazing—60 years after the double helix, we’re still discovering the basic properties of DNA,” said Dekker.


**Beating Drug-Resistant TB**

**Reinvestigating a natural antibiotic compound reveals its potential as a tuberculosis drug.**

*By Ruth Williams | September 19, 2012*

An antibiotic produced naturally by common soil bacteria kills *Mycobacterium* species that cause various human diseases, including tuberculosis (TB), according to a report published Monday (September 17) in *EMBO Molecular Medicine*. The antibiotic even kills drug-resistant strains that escape current TB treatments.

“I seldom get so tickled when I read a paper,” said William Jacobs, a microbiologist and immunologist at the Albert Einstein College of Medicine in New York, who did not participate in the research. The emergence of multidrug resistant strains of *Mycobacterium tuberculosis* “is a big problem,” he said. “This could be a godsend.”

Tuberculosis infections are commonly treated with a mixture of antibiotics, including one called isoniazid, which Jacobs described as “the cornerstone of TB therapy.” Unfortunately, the most common drug-resistant strains of *M. tuberculosis* are isoniazid-resistant, he said.

Many researchers, including Stewart Cole, chair of the microbial pathogenesis department at the École Polytechnique Fédérale de Lausanne in Switzerland, have thus been searching for new *M. tuberculosis*-killing drugs. “In the past we’ve been working a lot on TB drug discovery using target-based approaches... [but] this has been spectacularly unsuccessful,” said Cole. So instead, he and his colleagues looked back over decades of academic literature searching for reports of natural compounds with *M. tuberculosis*-killing activity.

They found pyridomycin. First described in the 1950s, the drug was reportedly produced by the bacteria *Streptomyces pyridomycticus* and *Dactylosporangium fulvum*. Surprisingly, little was known...
about pyridomycin—perhaps, Cole suggested, because isoniazid was discovered around the same time and simply stole the limelight.

Cole’s team grew cultures of *D. fulvum* bacteria, figured out how to isolate and purify pyridomycin, and then showed that the drug was indeed capable of killing *M. tuberculosis*, as well as many other *Mycobacterium* species, in culture.

This indiscriminate *Mycobacterium*-killing ability is a bonus, said Cole. “One of the problems with isoniazid is that it only works against TB,” he said. “If pyridomycin makes it into the clinic, it could have applications in leprosy or Buruli ulcer or atypical mycobacterial infections that can occur in cystic fibrosis patients.”

The team went on to identify the bactericidal target of pyridomycin—a protein called inhA, which is involved in synthesis of bacterial cell wall components. As it happens, inhA is the same protein targeted by isoniazid, but there is a difference in the two drugs’ mechanisms. While isoniazid is a pro-drug that requires activation by an intracellular enzyme called KatG before it can bind to inhA, pyridomycin binds inhA directly.

This is an important distinction, explained Valerie Mizrahi, director of the Institute of Infectious Disease and Molecular Medicine at Cape Town University, South Africa, who was not involved in the study. The overwhelming majority of drug resistance mutations in *M. tuberculosis* occur in the KatG gene, she explained, and such mutant strains should not be resistant to pyridomycin. Indeed, the team showed that clinical isolates of isoniazid-resistant *M. tuberculosis* carrying KatG mutations were killed effectively by pyridomycin. “The efficacy against drug resistant forms of *M. tuberculosis* is particularly encouraging,” Mizrahi said.

There is, however, much to be done before pyridomycin can be used in the clinic. “We would [need to] test that it works in animal models and that it is safe and doesn’t have any side effects,” said Cole. “That will take a couple of years.”

“It’s a long journey,” agreed Mizrahi, “but the big plus is that they don’t really need to validate inhA as a drug target because inhA is already the most well validated drug target out there... [so] it has got a good head start.”


**Opinion: What Is the Human Genome?**

**The human genome that researchers sequenced at the turn of the century doesn’t really exist as we know it.**

By Ken Weiss | August 17, 2012

The Human Genome project sequenced “the human genome” and is widely credited with setting in motion the most exciting era of fundamental new scientific discovery since Galileo. That’s remarkable, because in important ways “the human genome” that we have labeled as such doesn’t actually exist.

Plato essentially asserted that things like chairs and dogs, which we observe in this physical world, and even concepts like virtues, are but imperfect representations or instances of some **ideal** that exists, but not in the material world. Such a Platonic ideal is “the human genome,” a sequence of about 3 billion nucleotides arrayed across a linear scale of position from the start of chromosome 1 to the end of the sex chromosomes. Whether it was obtained from one person or several has so far been shrouded in secrecy for bioethical reasons, but it makes no real difference. What we call the human genome sequence is really just a **reference**: it cannot account for all the variability that exists in the species, just like no single dog on earth, real or imagined, can fully incorporate all the variability in the characteristics of dogs.

Nor is the human genome we have a “normal” genome. What would it mean to be “normal” for the nucleotide at position 1,234,547 on chromosome 11? All we know is that the donor(s) had no identified disease when bled for the cause, but sooner or later some disease will arise. Essentially all available whole genome sequences show potentially disease-producing variants, even including nonfunctional genes, in donors who were unaffected at the time.

Furthermore, the current reference genome sequence is haploid, which means that even if it were compiled from just one donor, the single reference sequence does not report the variation at millions of nucleotide positions between the donor’s two copies (except for X and Y) that we know exist. I understand that the DNA template is being resequenced, to be reported as a diploid sequence, which is progress. Hopefully this will be done in a way that produces **phased** sequence, in which each chromosome is reported separately, rather than just identifying the two alleles at each variable site along the genome without specifying on which chromosome it lies. Only the former format will represent sequences as they
actually exist in the sequenced person, identifying which alleles go together on a chromosome, and are thus linked evolutionarily.

Even so the reference human genome will keep changing! Corrections and refinements of problematic regions that are technically difficult to sequence are made, though nobody claims it will ever identify 100 percent of the 3.1 billion nucleotides without mistakes. But forgetting such minor errors, if such a diploid sequence were obtained from a single person, rather than a composite of several, one might think we finally have an actual set of sequences rather than a non-existent Platonic ideal. That would then be like the authorized type specimens of real plants and animals in museums.

Of course, biologists realize that it’s only a reference sequence, and they think of each of us carrying “copies” of the human genome referent, with some variants of that sequence. But even that idea is wrong. Calling them copies would be Platonic, as if our individual sequences came directly, if imperfectly, from this ideal as their shared template. More accurately, we should use a term like “instance” rather than copy. But a fundamental point is that the resemblance among instances is not due to descent from a single ideal, but for the evolutionary reason that they are homologous, that is, are from a chain of descent from the gene’s common ancestor. Homology is not the manifestation of an ideal, because the original ancestral instance really did exist.

Biologists take advantage of this fundamental fact of life when inferring ancestral sequences from the observed variation in today’s populations. One might suggest that instead of a rather arbitrary reference sequence from some donor, “the human genome” sequence should be this inferred ancestral sequence. But that doesn’t work either. The ancestral sequence for human genes usually goes back far beyond the origin of humans, and the ancestral sequences for each gene will have existed in vastly different times, places, individuals, and species. The intervening noncoding sequences between such genes, which is generally less constrained by natural selection, vary so much that we often can’t really guess their ancestral state. Further, genes have been rearranged among the chromosomes over time, so that gene A and B that are chromosomal neighbors in human genomes today may have been on entirely different chromosomes in the past, or vice versa. Finally, the ancestral gene may have been so different from today’s that using that as our reference would not serve the biomedical research community from a functional point of view.

The same is true to a lesser extent even among modern human genomes: in addition to single nucleotide variation, millions of bits of DNA large and small have been deleted, inserted, inverted, or rearranged in every human genome instance. This variation, and the variation that will continue to accrue in the human population, distances us from any single reference sequence even further.

Reference sets?
If a single reference sequence, even the ancestral sequence that really did exist, is problematic, could there be a better way? An appealing possibility is to use a set of DNA sequences, perhaps all known instances, to characterize human genomes. Instead of a single string, suppose we represented each part in the format of what is known as a gene or sequence “logo.” Here is an example:

This shows the relative frequency of each nucleotide at every point along the sequence. One would have to add a way to visualize insertions and deletions and so on, but computer technologies should be up to that task. If “The Human Genomes” sequence was portrayed in this way, we might replace our arbitrary type-specimen with more natural, biologically accurate, population thinking. Efforts are under way to create a biological reference along these lines.

Of course, a reference like this would have to be constantly updated, and still could not keep up with the changing frequencies at each position as people die and babies are born all the time. But there’s a more important and even deeper problem—with Platonic implications. Every time an individual cell divides, new mutations arise; no two cells even within any individual have the identical sequence. Because of this somatic mutation, the single sequence obtained from each individual is an imperfect representation even of that person’s genome. We can never know the variants in each of his/her billions of cells.

Coming to terms with Plato
We routinely use an arbitrary reference and/or ancestral sequences in our daily research. We develop phylogenies, and identify variation responsible for traits, including disease. We comparatively consult arbitrary references for humans and mice to design experiments that work only because of our evolutionary relationship. As limited human beings, we cannot grasp everything in our heads, and representations and reference guidelines are immensely useful.

In fact, in many ways, the human reference genome is an ideal, but not in the way Plato had envisioned ideal. In a deep and interesting way, he had things backward. His idea was that we are only
able to see imperfect images, of ideals that really have some separate existence. But actually, the ideals are neural constructs built inside our very material heads, and it is they that are imperfect representations of the actual world, not the other way round as Plato had it.

Thus, while any human reference genome may be far from perfect, it’s what we have to work with today, and it helps shed light on all aspects of human biology. Representations are fundamental to science. The danger is if we don’t understand them and they become misrepresentations.

Ken Weiss is a geneticist and evolutionary biologist at Penn State University. A fuller discussion of these points is available at The Mermaid’s Tale, a blog to which Weiss is a contributor.

comments

Dan Arel •
i would support a national project where everyone had their genome cataloged, for medical reasons, criminal reasons, but also, i think that we could learn so much if we had a sample size that large.
i don’t think it would be a very popular idea, but as someone with nothing to hide and since i don’t live in fear of govt conspiracies, i would be okay with it.

Sherry Lewis

Unfortunately, this is not the case for Aboriginal or Native Americans. The US government is using blood quantum to determine how much ‘Indian blood’ a person has and this determines how much Native American rights can be accessed.

Just imagine if this method was used to determine how much ‘American blood’ every American person has that has to be linked to the people who came over with Christopher Columbus and this then determined the American rights you can access.

As a First Nations person, I have nothing to hide, but it has never been in my best interest to allow the government to take control.

John P Remillard

IBM & National Geographic teamed up to capture as many human genes as possible. It is called the: Genographic Project

Dale Yuzuki

Speaking with a member of the 1000 Genomes Project analysis team a week ago about this topic, there is active work on refining the human reference sequence, along with an active discussion of whether there should be separate ethnicity reference sequences, which makes sense.

For those interested, here’s a GenomeWeb piece from 2009 about the 5 million bases missing from the reference. http://www.genomeweb.com/sequencings, all further sequence use the baselines as templates to “speed up assembly”.

We currently have not only a human reference genome but also a model of how to compare it to the genomes of other species. Within the confines of that model, we know that the epigenetic effects of nutrient chemicals and pheromones cause changes in intracellular signaling and stochastic gene expression. The changes in gene expression allow sensory input from the environment to cause speciation. We also know that olfaction and odor receptors provide a clear evolutionary trail that can be followed from unicellular organisms to insects to humans.

Clearly, the genetic predisposition of the first living cell allowed the required receptor-mediated events for food acquisition and stochastic gene expression, which are linked directly to the de novo production of additional chemical (i.e., odor) receptors. Those receptors are unequivocally required for adaptive evolution via ecological, social, neurogenic, and socio-cognitive niche construction.

If the molecular biology that is common to all species did not ensure that the epigenetic effects of nutrient chemicals and pheromones altered gene expression in every species we would have limited genetic variation instead of the variation that is obviously required to link us—via adaptive evolution—to the origins of the human reference genome. That is the representation we now have to work with. What we observe is genetic diversity that can be sniffed out, even if it cannot be seen.

As Decartes probably meant: I think I need to eat; therefore I am. And I am tired of misrepresentations and constructs that do not incorporate the molecular biology that is common to all species. The human reference genome did not suddenly materialize so that it could be sequenced. Did it?

Burt Lancaster Bizzarri

A more clear explanation of what a "Model" does mean for science and technology would have helped more then Plato’s comments.

Ellen Hunt

Ken, it’s way worse than that. The genome that was sequenced is a partial one and we know it. We didn’t sequence any chromosome in the region near the centromere because it was too hard. That’s about 5%-10% of the genome. Is that area inactive? Probably not. We depend on BLAST to be right, but know that there are parts of the genome where it is most certainly wrong. And since the first sequencings, all further sequences use the baselines as templates to "speed up assembly".

In other words, the genome we have is wrong and we know it. And we are using the first, known to be incorrect version to "correct" and as a scaffolding for everything after it.

But the "story" of completion is just too good, too compelling, to tell the truth. Wouldn’t be so good for grant writers would it?

And there was that infamous competition too.

I hatenow

check out this research group out of the University of Washington http://boinc.bakerlab.org/rose...

Getting to Know the Genome

A massive project involving hundreds of scientists suggests that very little—if any—of the human genome is truly non-functional.

By Ed Yong | September 5, 2012

In 2001, the Human Genome Project produced a near-complete readout of the human species’ DNA. But researchers had little idea about how those As, Gs, Cs, and Ts were used, controlled, or organized, much less how they code for a living, breathing human.

That knowledge gap has just got a little smaller. A massive international project called ENCODE, the Encyclopedia of DNA Elements, has cataloged every nucleotide within the genome that does something—
which, it turns out, is significantly more than the **1.5 percent of the genome contains actual instructions for making proteins.** The research, a 10-year effort by an international team of 442 scientists, shows that the rest of the genome—the non-coding majority—is still rife with “functional elements.”

“The genome is no longer an empty vastness,” said Shyam Prabhakar from the Genome Institute of Singapore, who was not involved in the study. “It is densely packed with peaks and wiggles of biochemical activity.”

“Almost every nucleotide is associated with a function of some sort or another, and we now know where they are, what binds to them, what their associations are, and more,” added Tom Gingeras, one of the studies’ many senior scientists. The results are published today (September 5), in more than 30 papers across many different journals.

Researchers **have long recognized** that some non-coding DNA probably has a function, and many **solid examples** have recently **come to light.** At the same time, people did believe that much of these sequences were, indeed, junk. The ENCODE project suggests otherwise.

The researchers found that **many non-coding parts of the human genome contain docking sites where proteins can bind, affecting the expression of both nearby and distant genes.** Other non-coding regions are transcribed into RNA molecules that are **never translated into proteins.** Still others affect how the DNA is folded and packaged. In sum, these regions are not just junk; according to ENCODE’s analysis, **80 percent of the genome has some biochemical function.**

The remaining 20 percent may not be junk either, according to Ewan Birney, the project’s Lead Analysis Coordinator. He explains that while ENCODE looked at 147 different types of cells, there are a couple of thousand in total. If other cell types are examined, functions may emerge for the phantom proportion. “It’s likely that 80 percent will go to 100 percent,” Birney said. “We don’t really have any large chunks of redundant DNA. This metaphor of junk isn’t that useful.”

The implications are vast, from redefining what a “gene” is to providing new clues in the quest to understand diseases and how the genome works in three dimensions. “There are nuggets for everyone here,” Prabhakar said. “No matter which piece of the genome we happen to be studying in any particular project, we will benefit from looking up the corresponding ENCODE tracks.”

Of course, there’s still a long way to go, Birney noted. “I think it’s going to take this century to fill in all the details,” he said. “That full reconciliation is going to be this century’s science.”

**By the numbers**

Researchers already knew that 1.5 percent of the genome codes for proteins. ENCODE found that an additional **8.5 percent codes for regions where proteins stick to DNA,** presumably regulating gene transcription. And, because ENCODE hasn’t looked at every possible type of cell or every possible protein that sticks to DNA, this figure is likely conservative. Birney **estimates that the total proportion of the genome that either creates a protein or sticks to one is around 20 percent.**

The rest of the functional elements in the ENCODE analysis cover other classes of sequence that were thought to be essentially functionless, including introns. “The idea that introns are definitely deadweight isn’t true,” said Birney. Even some repetitive sequences—small chunks of DNA that have the ability to copy themselves and are typically viewed as parasites—are likely to be functional, often containing sequences where proteins can bind to influence the activity of nearby genes. Perhaps their spread across the genome represents not the invasion of a parasite, but a way of spreading control. “These parasites can be subverted sometimes,” Birney said.

Birney expects that many skeptics will argue about the exact proportion—the 80 percent of the genome that ENCODE estimates to be doing something—and about the definition of “functional.” But, he said, “no matter how you cut it, we’ve got to get used to the fact that there’s a lot more going on with the genome than we knew.”

**What’s in a gene?**

The simplistic view of a gene is that it’s a stretch of DNA that is transcribed to make a protein. But with ENCODE’s data, this definition no longer makes sense. There are a lot of transcripts, probably more than anyone had realized, some of which connect two previously unconnected genes. This means that the boundaries for those genes have to widen, and the gaps between them shrink or disappear.

Gingeras says that this “intergenic” space has shrunk by a factor of four. “A region that was once called Gene X is now melded to Gene Y,” he says. With such blurring boundaries, Gingeras thinks that it no longer makes sense to think of a gene as a specific point in the genome, or as its basic unit. Instead,
that honor falls to the RNA transcript. “The atom of the genome is the transcript,” says Gingeras. “They are the basic unit that’s affected by mutation and selection.”

**New disease leads**

For the last decade, geneticists have run a seemingly endless stream of genome-wide association studies (GWAS), and have thrown up a long list of single nucleotide polymorphisms (SNPs) that correlate with the risk of different conditions. The ENCODE team has mapped *all* of these GWAS-identified SNPs to their data.

The researchers found that just **12 percent of known SNPs lie within protein-coding areas**. They also showed that compared to random SNPs, the disease-associated ones are 60 percent more likely to lie within the non-coding but functional regions that ENCODE identified, especially in promoters and enhancers. This suggests that many of these variants are controlling the activity of different genes, and provides many fresh leads for understanding how they affect our risk of disease. “It was one of those too good to be true moments,” said Birney. “Literally, I was in the room [when they got the result] and I went: Yes!”

The ENCODE researchers also found new links between disease-associated SNPs and specific DNA elements. For example, they found five SNPs that increase the risk of Crohn’s disease, and that are recognized by a group of transcription factors called GATA2. “That wasn’t something that the Crohn’s disease biologists had on their radar,” Birney said. “Suddenly we’ve made an unbiased association between a disease and a piece of basic biology.”

“We’re now working with lots of different disease biologists looking at their data sets,” he added. “In some sense, ENCODE is working from the genome out, while GWAS studies are working from disease in.”

So far, the team has identified 400 such hotspots that are worth looking into.

**The 3-D genome**

Writing the genome out as a string of letters invites a common fallacy: that it’s a two-dimensional, linear entity. In reality, DNA is wrapped around proteins called histones like beads on a string. These are then twisted, folded and looped in an intricate three-dimensional way. In this way, distant parts of the genome can actually be physical neighbors, and can affect each other’s activity.

Job Dekker, a bioinformaticist at University of Massachusetts Medical School, used ENCODE data to map these long-range interactions across just 1 percent of the genome in three different types of cell, and discovered more than 1,000 of them. “I like to say that nothing in the genome makes sense, except in 3D,” said Dekker. The availability of the new ENCODE data is “really a teaser for the future of genome science,” he added.

**Sharing the data**

The new ENCODE results are vast, reported in 30 central papers in *Nature, Genome Biology*, and *Genome Research*, as well as a slew of secondary articles in *Science, Cell*, and others. And all of the data are freely available to the public.

The pages of printed journals are a poor repository for such a vast trove of data, so the ENCODE team have devised a new publishing model. On the ENCODE portal site, readers can pick one of 13 topics of interest, such as enhancer sequences, and follow them in special “threads” that pull out all the relevant paragraphs from the 30 main papers. “Rather than people having to skim read all 30 papers, and working out which ones they want to read, we pull out that thread for you,” Birney said.

The team has also built what they call a Virtual Machine, a downloadable program that includes all the code that the ENCODE scientists used to analyze their data. Any researcher can download almost-raw data and reproduce any of the analyses in the papers by themselves. It’s the ultimate in transparency.

“With these really intensive science projects, there has to be a huge amount of trust that data analysts have done things correctly,” said Birney. With the virtual machine, “you can absolutely replay, step by step, what we did to get to the figure. I think it should be the standard for the future.”

**comments**

**Michael Holloway**

What’s old is new again. Nice to see how well the hits on the DNase hypersensitivity and Chip binding tracks line up. Could always see it happening in small regions in isolated studies, but here you can see it over large stretches.

**John Collins**

Thank you very much for this contribution, in particular including the direct link to the ENCODE portal. This is surprisingly intuitive to use, contains direct access to an enormous amount of information and is incredibly fast. Looking at the data I wonder a little at the conclusion that there is direct evidence for functionality of 80% of the genome. However, looking at evolutionary conservation between species and which regions have been allowed to undergo high random mutation/deletion/insertions and which regions have not, the conclusion would be expected.

**OBS**
Why don’t you talk about the fractal genome? Why don’t you explain that there are 2 DNA: n-DNA and mit-DNA? Why don’t you talk about mit-genome fractal dimension?

Andrew Pauls

What a wonderful leap forwards and what a jaw-dropping vista the new data affords. I can with even more confidence now tell my children that a career in genetics will sustain not only them, but also their children and grandchildren, for it seems likely that it will take at least three generations of scientists to unravel the full complexity. The engineer in me says that we end up with a massive master circuit diagram, full of nested loops and strange counter-intuitive circuit topologies. Stability analyses will have been performed against both internal and externally-induced perturbations.

Once this level of understanding is reached (the poles and zeroes if you will), we can then re-engineer the whole thing. It is almost certain that we can do a better job post hoc than the accretive methods used by Nature.

corrigible

The more energy we spend on accessing, documenting, measuring, comparing, analyzing... new data, the less time we will have for vacuous debates over things we have no data to support. The progress in genetics, epigenetics, proteomics... has been exhilarating in this century so far. Am currently reading “The Beak of the Finch,” by Jonathan Weiner, 1995, and discovering there is, after all, some hard data to support some aspects of current state of evolutionary theory. BRAVO! Too bad so many who are on both sides are unable to cite sources, such as this one, and make arguments based more on emotion than data or reason.

There are numerous interpretations of existing hard data in this book that are compelling, and some that strike me as a bit forced and bordering on dogmatic. But let me recommend that each and every person who wishes to argue in opposition to bioevolutionary theory AND every person who wishes to argue for it, read this book very thoroughly. That way, neither side will have to argue points on theoretical or common sense grounds only. There IS hard data. And this book is so beautifully and sensibly written that it is both hard to put down and enormously enlightening. Far more hard data is becoming available in genetics, epigenetics, proteomics, microbiology, there is little time for emotional or pseudo-common sense arguments. Hard data and objective reason are where answers in science come from—not from clashes of uninformed opinion. The way things ARE is the the way the ARE. And the more energy spent on discovering that, the less energy is spent in arguing over how many evolutionists it takes to screw in a light bulb. (Two, but it takes a rather large light bulb.)

jkohl

Darwin could not have argued for transgenerational epigenetic inheritance of behaviors associated with the obvious requirements of nutrient chemical-dependent reproduction controlled by pheromones in species from microbes to man, including his pigeons. Similarly, a 1995 book on finches could not have included anything about the importance of olfactory/pheromonal input to avian behavior. Thus, the two most necessary requirements for adaptive evolution via ecological, social, neurogenic, and socio-cognitive niche construction have not been included in discussions of genetics or evolved behaviors. A 1995 book on human pheromones would provide an excellent source of citations that bring us current to information available on genomic adaptation. See, for example, The Scent of Eros: Mysteries of Odor in Human Sexuality (1995/2002) as a guide to what has recently been detailed about adaptive evolution in the context of epigenetic effects on genetic predispositions that include genetically predisposed behaviors.


corrigible

So that’s what has driven human evolution from a common ancestor with the honey bee?

Eureka! If one person thinks he is the joker, and shoots up the audience in a movie theater, and another donates a kidney to someone he is not even kin to, that is because the ancestors of each, got a whiff of a different school of pheromonic impetus.

Gosh! And all along I’ve been suffering under the illusion that the explanation of the varieties of human behavior were more complex than that.

Whodathotit!!

Father’s Age Affects Mutation Rate

The number of new gene mutations in children rises dramatically with the age of their father at conception.

By Hayley Dunning | August 22, 2012

Estimates of overall human de novo mutation rate—the appearance of new gene mutations—have been largely carried out using indirect methods, such as extrapolating mutation rates from disease states or from the record of divergence of species. But whole genome sequencing is changing that, providing a way to map de novo mutations arising in family lines. Now, in a huge study that sequenced the genomes of 219 individuals consisting of 78 trios (father, mother, and child) and some multi-generational families, the rate of human mutations is clearer than ever, and surprisingly lower than previously estimated. However, according to the study, published today (August 22) in Nature, the number of mutations originating from the father rises with the age, so that the number of mutations doubles for every 16.5 years older the father is, raising the potential for detrimental mutations to occur and cause disease.

The results “are substantial and exciting given that this is the largest whole genome sequencing study of trios, relatives, or multigenerational pedigrees to date,” said geneticist Philip Awadalla of the University of Montreal, who was not involved in the study, by email. The sequencing was carried out by deCODE Genetics in Iceland, as part of a larger project aimed at understanding the contributions of the genome to human diversity, which has already sequenced the genomes of around 2,500 Icelanders. Iceland’s small population and impeccable records of genealogy make it ideal for population studies, and deCODE has also already genotyped 120,000 individuals.
The families sequenced for this study consisted of both disease-free children and children with disorders resulting from mutations, particularly autism spectrum disorder (ASD) and schizophrenia. While de novo mutations are random, the more mutations that accrue, the more likely one will be detrimental. Mutations were identified by comparing the genomes of the parents and their offspring, and although Awadalla is concerned that relatively few mutations were subject to experimental validation, he believes the potential for false positives doesn’t change the conclusions about human mutation rate and the link to father’s age.

Indirect approaches have estimated that the father’s contributions will be more mutated than the mother’s because of the difference between production of the sperm and ova. Sperm are generated and proliferate throughout a man’s life, whereas ova are likely all present from birth. The estimated difference in mutation rates between the sexes has been variable, but high, at around 4-7 times faster in males. This new study confirms that the variance is high, but that the father’s contribution of mutations is likely no more than two times greater than the mother’s.

The dependence on father’s age on mutation rate, however, is a “terribly novel” finding according to Awadalla. “The age dependence with respect to mutation rates in fathers is robust and the first direct observation from substantial numbers in humans without reliance on indirect approaches,” he said. “The observation is striking particularly for autism and schizophrenia families.” The risk of ASD and schizophrenia increased significantly with father’s age at conception, which the authors say is consistent with epidemiological studies in Iceland. Children with ASD in this study had no close genetic relatives with the disease, meaning the incidence of ASD is likely to be solely as a result of de novo mutations.

Factoring in father’s age over Iceland’s history, it appears the average age of fathers has been rising lately, from around 27 in the 1970s to 33 today. “Perhaps a sizeable portion of the increase in the diagnoses of autism over the past few years is rooted in the increasing age of fathers,” said deCODE CEO Kari Stefansson.

The determination of the human mutation rate overall also brings up new questions in human evolution. This study confirms the mounting evidence that mutation rate has likely been two or three times slower than previously estimated. The result is “fairly important as the rate of mutation is used to calibrate split times between species,” said Awadalla. “It appears that divergence times between humans and other primates is almost double that which was previously inferred from fossil records or phylogenetic approaches.” The rate at which species branch off could therefore be slower than previously estimated, shifting the timescales of human evolution.


comments

The metal iron is known to buildup in our bodies as we age. Age-related iron accumulation. Women are less effected because women have menses which allow them to lose much of this iron , until they reach menopause , when they begin to gain iron because they no longer lose the iron in their monthly blood loss .Men though have no way to lose this iron and this ‘age-related iron accumulation’ allows for the increased oxidation / rust which causes DNA mutation. "Oxidative DNA damage: mechanisms, mutation, and disease" http://www.fasebj.org/content/... Edward R. Mikol

The widespread use of ultrasound as a causative factor in the recent rise in autism should be studied since older men have been fathering kids for thousands of years.

Andre Pilon

"There is no independently confirmed peer-reviewed published evidence that a cause-effect relationship exists between in utero exposure to clinical ultrasound and development of ASDs in childhood." From J Ultrasound Med. 2012 Aug;31(8):1261-9. Ultrasound and autism: association, link, or coincidence?

Abramowicz JS.

Popular HIV drug may cause memory declines

Johns Hopkins study suggests the commonly prescribed anti-retroviral drug efavirenz attacks brain cells

The way the body metabolizes a commonly prescribed anti-retroviral drug that is used long term by patients infected with HIV may contribute to cognitive impairment by damaging nerve cells, a new Johns Hopkins research suggests.

Nearly 50 percent of people infected with HIV will eventually develop some form of brain damage that, while mild, can affect the ability to drive, work or participate in many daily activities. It has long been assumed that the disease was causing the damage, but Hopkins researchers say the drug efavirenz may play a key role.
People infected with HIV typically take a cocktail of medications to suppress the virus, and many will take the drugs for decades. Efavirenz is known to be very good at controlling the virus and is one of the few that crosses the blood-brain barrier and can target potential reservoirs of virus in the brain. Doctors have long believed that it might be possible to alleviate cognitive impairment associated with HIV by getting more drugs into the brain, but researchers say more caution is needed because there may be long-term effects of these drugs on the brain.

"People with HIV infections can't stop taking anti-retroviral drugs. We know what happens then and it's not good," says Norman J. Haughey, Ph.D., an associate professor of neurology at the Johns Hopkins University School of Medicine. "But we need to be very careful about the types of anti-retrovirals we prescribe, and take a closer look at their long-term effects. Drug toxicities could be a major contributing factor to cognitive impairment in patients with HIV."

For the study led by Haughey and described online in the Journal of Pharmacology and Experimental Therapeutics, researchers obtained samples of blood and cerebrospinal fluid from HIV-infected subjects enrolled in the NorthEastern AIDS Dementia study who were taking efavirenz. Researchers looked for levels of the drug and its various metabolites, which are substances created when efavirenz is broken down by the liver. Performing experiments on neurons cultured in the lab, the investigators examined the effects of 8-hydroxyefavirenz and other metabolites and found major structural changes when using low levels of 8-hydroxyefavirenz, including the loss of the important spines of the cells.

Haughey and his colleagues found that 8-hydroxyefavirenz is 10 times more toxic to brain cells than the drug itself and, even in low concentrations, causes damage to the dendritic spines of neurons. The dendritic spine is the information processing point of a neuron, where synapses — the structures that allow communication among brain cells — are located.

In the case of efavirenz, a minor modification in the drug's structure may be able block its toxic effects but not alter its ability to suppress the virus. Namandje N. Bumpus, Ph.D., one of the study's other authors, has found a way to modify the drug to prevent it from metabolizing into 8-hydroxyefavirenz while maintaining its effectiveness as a tool to suppress the HIV virus.

"Finding and stating a problem is one thing, but it's another to be able to say we have found this problem and here is an easy fix," Haughey says.

Haughey says studies like his serve as a reminder that while people infected with HIV are living longer than they were 20 years ago, there are significant problems associated with the drugs used to treat the infection.

"Some people do seem to have this attitude that HIV is no longer a death sentence," he says. "But even with anti-retroviral treatments, people infected with HIV have shortened lifespans and the chance of cognitive decline is high. It's nothing you should treat lightly."

Life-Threatening Meningitis Cluster in NYC HIV+ Men Sparks Warning

The New York City Department of Health and Mental Hygiene (NYCDOHMH) is investigating a cluster of potentially lethal invasive meningococcal disease among men who have sex with men (MSM), according to a news announcement.

Within the past four weeks, there have been four cases among MSM in the city, all of whom are HIV positive—one person died and another remains in critical condition. Over the past two years, an Associated Press story adds, there have been a dozen cases, a total of four of which resulted in death.

Invasive meningococcal disease is a severe bacterial infection that can cause meningitis (infection of the thin lining covering the brain and spinal cord) or meningococcemia (infection of the blood). The infection can also cause pneumonia or involve the joints, such as the knees.

Common symptoms of meningitis are high fever, headache, stiff neck and rash that develop rapidly within two days. People that have been in prolonged close contact with infected people need to see their health care provider to receive preventive antibiotics. Similarly, those experiencing symptoms—which usually occur within five days of exposure—should seek medical care immediately.