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Everything okay down there? Screening for anal cancer (long)

Published: 17 July 2011

Anal cancer is around 50 times more common in gay men with HIV than it is in the general population. Should we be demanding screening and vaccinations? Gus Cairns investigates.

In May 2009, HTU wrote about cervical cancer in women with HIV (Cervical cancer and you, HTU 186).¹ That article quoted recommendations for “aggressive” annual screening for cervical cell changes, because women with HIV were twice as likely to be infected with the human papillomavirus (HPV), the virus that causes the cancer, three to four times more likely to develop pre-cancerous abnormal cells, and twelve times more likely to get invasive cervical cancer if they do.² If they do get cancer, there is a one in three chance they will be dead of it within ten years.³ But a simple procedure under local anaesthetic can remove pre-cancerous cells if they are identified – and the national screening programme has cut mortality by nearly two-thirds.⁴ And we now have a vaccine against the two most common cancer-causing varieties of HPV, with a programme to give that vaccine to all teenage girls.

Anal cancer is caused by the same virus and, in the same way as cervical cancer, causes pre-cancerous changes in cells that can be screened for and treated. It’s about 16 times rarer than cervical cancer in the general population. But it’s about 60% more common in women than men and about 50 times more common in gay men with HIV (because anal sex is a risk factor) – which makes it as common in them as cervical cancer is in HIV-positive women and is a huge risk increase: for comparison, lung cancer is ‘only’ 25 times more common in heavy smokers than in non-smokers.⁵ If you do develop anal cancer, there’s a one-in-three chance you’ll die of it within five years.⁶,⁷

But, unlike the regular check-ups for cervical cancer in women, there is no standard screening for anal cancer, or even any agreement about whether it would be a good thing. And although the HPV vaccine has been licensed for use in boys in the US, a licence for this use has not been granted in Europe. Why not? Should we be agitating for better screening – especially of gay men with HIV – for anal cancer and for extending the HPV vaccine to boys?

HPV and anal cancer – the facts

Cervical and anal cancers are caused almost entirely by a viral infection – HPV – which is not one virus, but a family of about 100 different ones that cause everything from common warts to genital warts to cancers. The majority of sexually active adults eventually acquire at least one variety of HPV and it’s a near-universal infection in people with HIV. For the majority of people HPV has no symptoms.
Only specific varieties of HPV – the so-called ‘high-risk’ types – cause cancers. HPV 16 is the most common as an infection and is associated with the highest rate of progression to cancer. The second most common and aggressive type in the US and Europe is HPV 18. There are at least twelve other high-risk types, some of which are more common than type 18 in other parts of the world but tend to be less aggressive. Types 16 and 18 between them cause 70% of cervical cancers and 80% of anal cancers worldwide.\(^8\)

One important fact about HPV is that, in most cases, the body eventually gets rid of the infection. The average length of any single anal HPV infection is five months to a year in HIV-negative people: people with weaker immune systems may take longer to get rid of it.\(^9\)

Anal cancer differs from cervical cancer in that there is less association between CD4 count and risk, although people with lowered immunity are at greater risk of anal cancer. Most of the increased prevalence is amongst gay men regardless of HIV status.\(^10\) This may be due to more frequent infection with a greater variety of types of HPV, largely due to anal intercourse. HIV therapy is not reducing HPV incidence. A recent French study found that 98% of gay men diagnosed with HIV already had evidence of at least one HPV type, 92% a high-risk type and 43% HPV 16; after two years on HIV therapy these percentages were not significantly lower.\(^11\)

There are now two HPV vaccines, Merck’s *Gardasil* and GlaxoSmithKline’s *Cervarix*. Both vaccines protect against infection with HPV types 16 and 18, and *Gardasil* against the two most common low-risk genital wart varieties too (HPV 6 and 11).

**Testing and grading**

The high-risk HPV types tend not to cause obvious genital warts but do cause changes to the appearance and function of cells in the anal canal, which can be seen under medical examination. Areas either lose all pigment and look white, or get hyperpigmented and look red. While only a tiny proportion of people with HPV will go on to develop cancer, these changes are very common and can be graded by severity. Two grading categories are used, according to the type of medical test done.

In a *smear test*, some cells from the anal region are swabbed off with a sample stick. These cells are suspended in fluid, stained and examined under a microscope, a process called *cytology*. Cells modified by HPV often have larger or multiple nuclei, thicker walls and a generally ‘denser’ appearance. Cells are graded according to their individual appearance into: normal; ‘atypical squamous cells of undetermined significance’ (ASCUS); and low- and high-grade ‘squamious intraepithelial lesion’ (LSIL and HSIL). If they are fully-fledged cancer cells, but there is no invasive cancer, the diagnosis may be adenocarcinoma in situ (AIS).

In an *anoscopy*, the physician will visually examine the anal region in more detail using a proctoscope, and take biopsies: small snips of whole tissue. These will then be examined under the microscope in a process called *histology*, which looks at changes in the whole tissue and how it is organised, rather than at individual cells: for instance, what proportion of cells in the biopsy have become atypical and whether the lesion just affects the epithelium – the surface membrane of the anal tissue – or has penetrated to deeper areas. Any lesions are then graded into anal intraepithelial neoplasia (AIN), grades 1, 2 or 3.

Cytology is sensitive – it is good at picking up signs of pre-cancerous changes in cells – but HPV specialists at the Chelsea and Westminster Hospital found that it only correctly predicted the AIN grade in 40% of cases.\(^12\) This is in contrast to cervical cytology in screening, which is over 90% specific.\(^13\) So, while a smear test may be the cheapest and most convenient way of screening for possible anal cancer, an anoscopy is the only way to decide if changes warrant treatment. For the types of treatment people can be given, see below.

**Screening**

Given the comparative rarity of anal cancer, screening the general public is not considered necessary. But for those at higher risk (gay men with HIV, possibly all gay men and women who have anal sex), cervical screening is a good precedent for the value of anal screening. In the UK, cervical screening is offered to women aged 25 to 65. The death rate due to cervical cancer in women under 45 went down by nearly two-thirds between 1988, when screening was introduced, and 2002, despite there being an increase in genital wart diagnoses at the same time.\(^14\)

So surely we should be trying to do the same for anal cancer?

Professor Mark Bower is a consultant at London’s Chelsea and Westminster Hospital, specialising in HIV-related cancers. Though in favour of people with HIV having regular anal screening, he says that the case for it being routine is surprisingly hard to make.
That’s partly because it’s still relatively rare. In the Chelsea and Westminster cohort, they have seen 60 cases in 11,112 patients (one per 188 patients) throughout the clinic’s history, but this includes patients coming to the hospital specifically to see HPV and anal cancer specialists. In patients attending the Chelsea and Westminster’s general HIV clinic, they see fewer than one new case a year.

This may seem odd, given that rates of AIN are very high. For instance, one study of HIV-positive men found that despite AIN grades 2 or 3 being found at least once in 133 of the 247 patients in the study (54%), there were only two cases of anal cancer in three years.15

We don’t know exactly why some anal (or cervical) lesions turn into an invasive cancer, and others don’t. Bower has evaluated the cases of nearly 1000 HIV-positive men who have sex with men seen over the last ten years at the Chelsea and Westminster.

“These guys’ AIN grade goes up and down and up again,” he says. “A lot of them have been coming here for ten years and show no signs of progressing.”

This is partly due to the natural history of HPV and the fact that infections regress as often as they recur. Most AIN grade 1 lesions simply disappear and only a minority progress to higher grades. We don’t even know the rate at which high-grade AIN lesions change into anal cancer: estimates vary hugely from 0.2 to 12.5% a year (the consensus is between 1 and 5%). The thing that keeps lesions coming back in gay men is not persistent HPV infection but reinfection; in HIV-positive gay men, persistent infection adds to the risk.

Or incidence of anal cancer may be lower than expected because, in many patient cohorts, gay men with HIV are already being screened regularly. Even in cervical cancer, it has been difficult to calculate the benefit of national screening because so much ad hoc screening was being done before the national programme began.

“Maybe it’s because of our excellent interventions,” says Bower, “or maybe it’s because progression to cancer just doesn’t happen in most people with AIN.” There has never actually been a randomised controlled trial of cervical cancer screening, and there couldn’t ethically be one of an HPV-associated cancer now: would you allow your doctor to ignore pre-cancerous cell changes to see if they turned into cancer?

Another problem is cost-effectiveness.

There have been two studies in the US, showing that screening would be relatively cost-effective in both HIV-negative and HIV-positive gay men. In the cost-effectiveness study in HIV-positive gay men, the cost per quality-adjusted life-year (QALY) saved was $16,000 with annual screening and $13,000 if done every two years.16 In HIV-negative gay men, the cost was considerably greater if you screened annually ($34,800) but comparable if done biennially ($15,100).17

However, a UK cost-effectiveness model found that national screening of gay men (with or without HIV) was unlikely to be cost-effective, with an average cost per QALY gained of £39,405, which is way beyond the usually quoted NICE (National Institute for Health and Clinical Excellence) threshold of £30,000.18 It was actually more cost-effective to screen all gay men in this study, rather than just the HIV-positive ones.

This model, however, contained a number of different assumptions from the US models. In the US, it was assumed that annual rate of transition from high-grade AIN to anal cancer was high: from 3.6 to 5% a year. Actual surveys suggest a lower rate of progression. The UK study assumed a much lower rate: about one case of anal cancer per 500 cases on untreated AIN grades 2 or 3 (0.2%), or one case per 2500 treated cases. This is probably on the low side, and there have been a number of other criticisms levelled at the UK paper, such as the assumption of a high rate of regression from AIN 1 to asymptomatic.

Screening gay men for anal cancer and its precursors has not been recommended in UK guidelines. The British HIV Association’s cancer guidelines of 2008 state: “there is little evidence for routine [screening] as the early detection of lesions still poses substantial difficulties and single biopsies may miss areas of AIN, with histology and cytology yielding some discordant results.”19

In complete contrast, US guidelines – such as those from New York State20 – recommend “anal cytology at baseline and annually”, especially for men with HPV or anal warts, and the European AIDS Clinical Society (EACS) guidelines recommend a rectal examination and/or smear every one to three years for gay men.21 Anoscopy would be reserved for people with abnormal cytology results, and the New York guidelines estimate that this would be less than 30% of the screened population.
Treatment
One of the reasons screening is not nationally adopted in the UK is because, to quote the BHIVA guidelines, “Treatment options for AIN are limited by morbidity and high recurrence rates.” That probably isn’t as true as it was. The becoming-standard treatment for AIN is infrared coagulation therapy (ICT) which involves burning off the affected areas with a heat gun. That sounds very painful, but can be carried out under local anaesthetic, causing only a couple of days’ discomfort. High recurrence rates are still a problem: after one treatment, 50% of HIV-negative gay men and 65% of HIV-positive ones had recurrent lesions within ten months. Until we get more data, we don’t know if these treatments are preventing progression to cancer – or just subjecting people to unnecessary discomfort.

If you are one of the unlucky few who get anal cancer, it’s not the end of the world. With a survival rate of 65% at five years, anal cancer looks bad compared to testicular cancer (97% alive at five years), but very good compared to advanced lung cancer (5% alive at five years). Surgery is not necessary for the majority of people if anal cancer is diagnosed before it becomes invasive. The standard treatment is radiotherapy, plus the anti-cancer drugs mitomycin C and capecitabine, or cisplatin – the kind of drugs that are much more tolerable these days, thanks to anti-emetic drugs.

Less easy to get on with is the radiotherapy, which involves a daily visit to the clinic for six weeks, and causes proctitis (anal and rectal inflammation and pain) for another six weeks or so after that. After these treatments it’s the usual watchful wait to see if it’s really gone or if it recurs.

About that vaccine...
What about getting yourself vaccinated? And should we be vaccinating adolescent boys as well as girls anyway, in case they get HPV 16 or 18?

In January this year, the US Food and Drug Administration approved the use of Gardasil to prevent anal cancer in people (of both sexes) between the ages of 9 and 26. So far, the European Medicines Agency (EMA) has not followed suit. In the decentralised healthcare system of the US, this is by no means a guarantee that your healthcare system will agree to pay for Gardasil, but it does mean that people who fall within the age criteria have a fighting chance. In a system like the UK’s NHS, EMA approval would only be the first step anyway, as medicines then have to undergo the eagle-eye scrutiny of our health technology assessment agency NICE, before the NHS will agree to provide it for free (and, for reasons of cost, the NHS approved Cervarix for vaccinating adolescent girls, not Gardasil).

The US approval followed a study22 that found that Gardasil had 65% efficacy in preventing anal lesions caused by the four types it immunises against in young men aged 19 to 26. That was for all the men who entered the study – and some who were already infected with HPV 16 or 18. The efficacy in men not already infected when they entered the study was 90%.

However, this tells us nothing about whether Gardasil really prevents anal cancer or even AIN – because nearly all the anal lesions seen were anal warts caused by types 6 and 11.

If you’re older and gay, surely it’s too late to vaccinate? Well... not necessarily, because the body can get rid of HPV infections, remember. There is very little research in this area, but a 2009 study largely of gay, HIV-positive, male US Army veterans found that 43% did not have antibodies to HPV types 16 or 18.23 This could mean they’d just been infected and not yet developed an antibody response, but it could also mean they’d never been infected or had got rid of their infection. An HPV DNA test would tell.

So might you benefit from getting the vaccine? Only if you can find out which HPV types you have and if you’ve never had type 16 or 18. In theory the HPV vaccine could protect you from reinfection but we don’t know whether it actually does. The vaccine has no effect on current infections. You’ll only get it done privately at present and, at £480 for a three-shot course of Gardasil (Cervarix costs about £315 privately) I is not cheap, and that’s not counting the costs of consultation and testing.

Conclusion
So what’s a boy to do who is worried about HPV and anal cancer, possibly because he’s had anal warts? “You should get screened annually and if you’re diagnosed with any lesions, you should ask for a referral to a specialist centre like ours,” is Mark Bower’s conclusion. The same would also apply if you are an HIV-positive woman who has anal sex. There’s an inevitable contradiction here: while UK cost-effectiveness modellers still come out against anal screening as standard for people with HIV, on an individual level, it is wise to talk to your doctor about getting yourself checked out with a smear test.

You may also want to do a regular self-examination of your anus, although in most cases the lesions caused by high-risk HPV strains tend to be flat and you won’t be able to feel anything. But if you do feel anything lumpy, you should certainly have it seen by a doctor as soon as possible. Other symptoms to report promptly are abnormal discharge or bleeding from the anus, itching, pain or pressure around the
anus, and anal sores that do not heal. (These symptoms can also be caused by other, more common, problems.)

In a world where HIV therapy is relatively standardised, the mess of contradictory evidence and recommendations around anal cancer thrusts us back to the time when HIV treatment itself was experimental and controversial, and you had to hunt for a hospital that agreed that viral load tests were cost-effective. Keeping yourself safe from anal cancer is one area where patient power makes a difference, and it pays to demand the best service. Get your rear end checked out regularly, and don’t die of embarrassment.

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Government Will Comply with Drug Site Ruling
Canadian Press, (09.30.2011) Mike Blanchfield

On Friday, the Supreme Court of Canada ordered the federal government to grant Vancouver’s supervised injection facility an exemption to federal drug laws. The 9-0 vote ordered the government to abandon its effort to close Insite, rebuffing the administration’s claims that the facility fosters addiction and runs counter to the government’s crime-fighting policies.

Based in Vancouver’s Downtown Eastside, Insite provides a facility where drug users can obtain sterile needles and water to inject illicit drugs while under the supervision of nurses. Insite was launched in 2003 as a pilot program exempted from federal drug laws under a previous, more liberal administration. Prime Minister Stephen Harper’s administration in 2008 signaled its intention to close Insite.

Supporters cited peer-reviewed studies showing Insite prevented overdose deaths and curbed injection-related infections, crime, and open drug use.
Canada’s Supreme Court ruled that preventing injection drug users from accessing Insite on the basis of federal drug laws would undermine the purpose of those laws: the protection of health and public safety.

“This limit is not in accordance with the principles of fundamental justice,” said Chief Justice Beverley McLachlin, author of the ruling. “It is arbitrary. It is also grossly disproportionate: the potential denial of health services and the correlative increase risk of death and disease to injection drug users outweigh any benefit that might be derived from maintaining an absolute prohibition on possession of illegal drugs on Insite’s premises.”

“The discretion vested in the minister of health is not absolute; as with all exercises of discretion, the minister’s decisions must conform to the charter,” said McLachlin.

“We’re disappointed,” said Harper. “We’ll take a look at the decision but we will clearly act in respect and within the constraints of the decision.”

**Fertility Intentions of HIV-Infected Women in the United Kingdom**

*AIDS Care Vol. 23; No. 9: P. 1093-1101, (09..2011)*  
Susan Cliffe; Claire L. Townsend; Mario Cortina-Borja; Marie-Louise Newell

In the current study, the authors sought to explore fertility intentions among HIV-positive UK women and to assess the effect of HIV treatment, as well as interventions to prevent mother-to-child transmission, on these intentions. The team noted that while the United Kingdom has seen a dramatic increase in the number of pregnancies among HIV-infected women during the past decade, attitudes toward childbearing among these women have not been described previously.

The subjects of the study were HIV-positive women, ages 16 to 49, who attended one of seven UK HIV clinics between July 2003 and January 2004. The women were asked to complete a questionnaire that collected information on demographic factors, history of HIV testing, history of pregnancy, and fertility intentions (i.e., the desire to have children).

A total of 521 women were eligible, of whom 450 (86 percent) completed the questionnaire. Three-quarters (336/450) reported they wanted (more) children; 45 percent (201/450) said their HIV diagnosis did not affect their fertility intentions; 11 percent (50/450) said the diagnosis made them want children sooner; 10 percent (44/450) did not know, or reported other views.

While one-third (155/450) of the women decided they no longer wanted children after learning they were HIV-positive, 41 percent (59/144) changed their mind due to advances in HIV management and treatment. “Factors associated with an increase in fertility intentions after advances in HIV management and treatment were being in a partnership and having fewer than two children,” the authors wrote.

“In this survey of HIV-infected women, the majority wanted children, and women were more likely to want children after improvements in HIV management and treatment. These findings highlight the need for specialized family planning and reproductive health services targeting this population,” the authors concluded.

**Cholera Death Toll In Haiti Rises To 6,435; U.N. Official Says Hardships Remain In Camps**

Haitian health authorities on Friday said the death toll from cholera has risen to 6,435 since October and that "the number of people infected with cholera almost reached half a million, although the ministry repeated the epidemic was decreasing," *Xinhua* reports (9/30). U.N. Under-Secretary-General for Humanitarian Affairs Valerie Amos wrapped up a three-day visit to Haiti on Friday, saying the "number of internally displaced persons (IDPs) still in camps in Haiti after their homes were destroyed by last year's catastrophic earthquake has declined from 1.5 million to 600,000, but hardship in the settlements has not eased," the *U.N. News Centre* reports. "Limited funding has led to a decline in the number of humanitarian agencies working in key sectors, such as water and sanitation and camp management. Hundreds of latrines are now unusable and overflow, especially during the current rainy season, posing significant health risks, even as efforts to keep the cholera epidemic at bay continue," the news service writes (9/30).

**Central African Republic Declares New Cholera Outbreak**

Central African Republic Health Minister Jean-Michel Mandaba on Friday declared a new outbreak of cholera in the south of the country had already killed at least 10 people, *Agence France-Presse* reports. "Mandaba also urged the country's 'bilateral and multilateral partners' to provide financial and technical
aid," the news agency writes. Health officials two months ago warned of a possible outbreak because of cases in nearby countries, according to the news agency (10/1).

**IPS Examines The Practice Of Breast Ironing In Cameroon**

*Inter Press Service* reports on the practice of breast ironing in Cameroon, a custom carried out by one-quarter of mothers in the country that is meant to reverse female sexual development in an effort "to avoid sexual contact between young girls and boys." The news service writes, "An estimated one in four girls suffers from the practice in their childhood. Breast ironing is a traditional ritual in which, by using heated and flat objects, a girl's growing breasts are pressed in order to suppress and reverse their development."

"Apart from being painful and psychologically traumatic, breast ironing exposes girls to multiple health problems. According to many medical reports, it can lead to abscesses, itching, inability to breastfeed ... babies, infection, deformity or disappearance of the breasts, cysts, tissue damage and even breast cancer," IPS writes. However, the news service notes, " Burning girls' emerging breasts to many mothers seems a far better option than the risk[s] of ... unwanted pregnancies, unsafe abortions, possible rapes or the transmission of sexual diseases" (Ortiz, 10/1).

**New Factor in HIV Infection Uncovered**

*ScienceDaily* (Oct. 2, 2011) — A George Mason University researcher team has revealed the specific process by which the HIV virus infects healthy T cells—a process previously unknown. The principal investigator, HIV researcher Yuntao Wu, says he hopes this breakthrough will start a new line on inquiry into how researchers can use this knowledge to create drugs that could limit or halt HIV infection.

Wu, a professor of molecular and microbiology at Mason, published these findings in an April 2011 edition of the *Journal of Biological Chemistry*, along with researchers Paul J. Vorster, Jia Guo, Alyson Yoder, Weifeng Wang, Yanfang Zheng, Dongyang Yu and Mark Spear from Mason's National Center for Biodefense and Infectious Diseases and the Department of Molecular and Microbiology and Xuehua Xu from Georgetown University School of Medicine's Department of Oncology.

This paper outlined a new understanding on how T cells—which are the target cells that the HIV virus infects—move and migrate when hijacked by the virus.

"The discovery adds to our understanding of how HIV initiates the infection of human T cells, which leads to their eventual destruction and the development of AIDS," Wu says.

Researchers and doctors have known for some time that the HIV virus, rather than directly killing healthy T cells, actually hijacks them. This eventually leads to their destruction. So the virus essentially turns the infected T cells (also known as CD4 T cells or helper T cells) into a factory for creating even more HIV. Learning more about how the cells are infected could be a key step toward figuring out how to stop infection altogether.

Wu's latest discovery builds upon his previous work, published in the journal *Cell* in 2008, which described the basic process of how HIV infects T cells. After discovering that coflin—a protein used to cut through a cell's outer layer, or cytoskeleton—is involved in HIV infection, Wu's new research provides the detailed framework for this process.

This new factor is called LIM domain kinase, or LIMK. The researchers discovered that LIMK triggers a cell to move, almost acting like a propeller. This cell movement is essential for HIV infection. This discovery marks the first time that a research team has uncovered the involvement of LIMK in HIV infection.

Building upon these results, the researchers then used a drug to trigger similar LIMK activation and found that it increased infection of T cells. Of course, the researchers ultimately want to decrease the infection of T cells—so they worked backwards and found something very promising.

"When we engineered the cell to inhibit LIMK activity, the cell became relatively resistant to HIV infection," says Wu. In other words, the researchers engineered human T cells that were not easily infected by HIV. This finding suggests that, in the future, drugs could be developed based on LIMK inhibition.

And while there are currently no medical drugs available to inhibit LIMK, Wu hopes this is a developing area in potential new therapeutic targets. One advantage of using this kind of therapy over the current medication available to those with HIV is that it's more difficult for the HIV virus to generate resistance to treatment, Wu explains.
Wu's team continues its work on decoding this complicated process, and he stresses that there is still much to be done.

"These findings are certainly exciting, and are an emerging research field that we are proud to have established three years ago with the publication of our Cell paper," he says. "We will continue to study the molecular details and to use those discoveries to develop new diagnostic and therapeutic tools to monitor and treat HIV-mediated CD4 T cell dysfunction and depletion."

**Journal Reference:**

### 'Master Key' to Unlock New Treatments for Autoimmune Disorders Discovered

ScienceDaily (Oct. 1, 2011) — Imagine a single drug that would treat most, if not all, autoimmune disorders, such as asthma, inflammatory bowel disease, and Lupus. That might not be so hard to do thanks to a team of researchers who have discovered a molecule normally used by the body to prevent unnecessary immune reactions. This molecule, pronounced "alpha v beta 6," normally keeps our immune systems from overreacting when food passes through our bodies, and it may be the key that unlocks entirely new set of treatments for autoimmune disorders.

This discovery was recently published in research report appearing the Journal of Leukocyte Biology. "Currently we do not have special methods to radically treat most immune diseases; all we can do is to temporarily inhibit the clinical symptoms for those diseases," said Ping-Chang Yang, a researcher involved in the work from the Department of Pathology and Molecular Medicine at McMaster University in Ontario, Canada. "Our findings have the potential to repair the compromised immune tolerant system so as to lead the body immune system to 'correct' the ongoing pathological conditions by itself."

Scientists made this discovery in mice when they noticed that their intestines secreted alphavbeta6, when absorbing food. Alphavbeta6, together with the absorbed food, induced the body to produce immune tolerant cells, which ensured that the food did not cause an excessive immune reaction. Researchers then generated alphavbeta6 using cultured intestinal cells and found that both could be used to generate the immune tolerant cells needed to reduce or eliminate out-of-control immune reactions.

"Development of new treatments and cures for diseases is usually a long process involving a series of incremental steps taken from the laboratory all the way through to the patient's bedside," said John Wherry, Ph.D., Deputy Editor of the Journal of Leukocyte Biology. "Occasionally, however, scientists make large leaps forward instead. While considerable work remains to determine whether or not this discovery will directly translate into new therapies, the alphavbeta6 discovery reported by these scientists is exciting, if not stunning."

**Journal Reference:**

### Previously Unknown Cell Interaction Key in Immune System Attacks

ScienceDaily (Oct. 2, 2011) — Most of the time, the immune system is the body's protector, warding off invading viruses and bacteria before they can lead to infection and disease. But in autoimmune diseases, the immune system does an about face, turning on the body and attacking normal cells.

A major discovery by La Jolla Institute scientist Amnon Altman, Ph.D., and his colleagues, of a previously unknown molecular interaction that is essential for T lymphocyte activation, could have major implications for stopping this aberrant immune system behavior and the accompanying undesirable immune responses that cause autoimmune diseases and allergies.

"Dr. Altman's finding is a breakthrough in our understanding of the complex biochemical changes that trigger the immune system's T lymphocytes, which are disease-fighting white blood cells, to mount an immunological attack," said Mitchell Kronenberg, Ph.D., president & chief scientific officer of the La Jolla Institute, an international leader in immunology research. Dr. Kronenberg said the discovery opens the door to the potential development of new therapies for multiple sclerosis, rheumatoid arthritis and a host of other autoimmune diseases by blocking the cellular interaction identified by Dr. Altman, thereby shutting off the unwanted immune attack.

The findings were published online October 3 in the journal Nature Immunology in a paper entitled "A motif in the V3 domain of the kinase PKC-0 determines its localization in the immunological synapse and functions in T cells via association with CD28." The immunological synapse refers to that region of
the T cell (also called T lymphocyte) membrane, which contacts antigen-presenting cells to initiate an immune response, and where many of the early activation events take place. La Jolla Institute scientist Kok-Fai Kong, Ph.D., was first author on the paper and Dr. Altman was senior author. Scientists from Japan and Israel also collaborated on the study.

Specifically, the findings provide new information about an enzyme—protein kinase C theta (PKC-θ)—discovered by Dr. Altman in humans in 1993 and known to be important for the activation of T lymphocytes. In 1997, scientists from the National Jewish Center for Immunology in Denver showed that PKC-θ is recruited to the immunological synapse when T cells encounter a foreign antigen. However, what has remained unknown ever since is the molecular basis for this recruitment and whether this is necessary for proper T cell activation.

Dr. Altman and his team set out to map the part of the PKC-θ enzyme involved in its recruitment, or co-localization, with the immunological synapse. They ended up identifying a previously unknown physical interaction that is key to this process between PKC-θ and CD28, a T cell stimulatory receptor, which has been known for a long time to be required for effective T cell activation. "We identified a small region of the enzyme, called the V3 region, that binds CD28, and demonstrated that this binding is critical for the enzyme's unique localization and its function," said Dr. Altman.

Christopher E. Rudd, Ph.D., a Professor of Molecular Immunology and Head of the Cell Signaling Section at Cambridge University, called the discovery a "big advance" in knowledge, with therapeutic implications. "Dr. Altman has mapped a novel interaction between PKC-θ and CD28, and has shown that this specific region modulates the immune system response to antigens," he said. "This now means that this region in PKC-θ can be targeted by novel therapeutics, or that protein fragments of the region itself could be used to treat a variety of immune disorders."

Dr. Rudd added that the finding brings the work of Dr. Altman full circle. "Many people discover something and then other scientists build on their discovery," said Dr. Rudd. "In Dr. Altman's case, not only was he the first to discover the PKC-θ enzyme, which served as an important tool for numerous groups around the world, but he has now discovered a new mechanism by which PKC-θ regulates immune function. He's drawn a circle around his initial discovery by outlining its importance and how it works. This will have an important impact on the field immunology."

Dr. Altman said efforts to develop small molecule drugs to block the PKC-θ enzyme's activity have been ongoing at several drug companies based on the previous knowledge of the enzyme's importance in T cell activation. "Here, we have found an alternative way of blocking the function of PKC-θ, not by inhibiting its enzymatic activity, but by inhibiting its recruitment to the immunological synapse, which is that part of the cell where it needs to be to activate T cells," he said. "Essentially, the enzyme remains fully active, but it can't trigger T cell activation because it's not in the right place in the cell."

Dr. Altman said that targeting the interaction between PKC-θ and CD28 in T cells is likely to be highly selective and, therefore, have minimal undesirable side effects on other cells and tissues because "T cells are the only cell type where the PKC-θ enzyme and CD28 are expressed together."

He noted, however, that creating a way to therapeutically block the binding of PKC-θ to CD28 is not an easy task, and will require creative strategies and diligence. "Several possibilities exist, such as using a peptide to block the interaction. However, getting a peptide into a T cell is not a trivial matter," said Dr. Altman. "While we consider our finding very promising, we know that developing a therapeutic to block this interaction is not something that will happen next year. It will take time, but the potential is exciting."

Journal Reference:
Kok-Fai Kong, Tadashi Yokosuka, Ann J Canonigo-Balancio, Noah Isakov, Takashi Saito, Amnon Altman. A motif in the V3 domain of the kinase PKC-θ determines its localization in the immunological synapse and functions in T cells via association with CD28. Nature Immunology, 2011; DOI: 10.1038/ni.2120

Non-surgical device provides safe and effective circumcision without need for anaesthetic or stitches
Michael Carter
Published: 04 October 2011
A device that provides non-surgical male circumcision without anaesthetic or the need for stitches is effective, safe and can be used in non-sterile environments, investigators from Rwanda report in the online edition of the Journal of Acquired Immune Deficiency Syndromes.

The single-centre study involved 55 young men who were circumcised using the PrePex device. This uses fitted rings to clamp the foreskin, leading to the death of tissue in the foreskin, which is then removed bloodlessly.
“The PrePex device applies controlled radial elastic pressure and hence requires no anesthesia,” write the investigators. “Use of the PrePex device is a nonsurgical procedure that can be performed in a standard consultation room, because the distal foreskin is necrotic when removed, bloodlessly.”

Randomised controlled trials have shown that circumcised men have their risk of infection with HIV reduced by between 53% and 60%. Both the World Health Organization and UNAIDS recommend consideration of male circumcision along with other preventative measures in countries with large, generalised and predominately heterosexual epidemics.

Only 15% of Rwandan men are circumcised. However, the government has plans to circumcise up to 2 million men. Given the country’s limited resources this will be difficult to achieve unless a non-surgical method of circumcision that can be performed by nurses in a non-sterile environment is found.

A method of male circumcision that could meet these requirements is the PrePex device.

Investigators at the Kanobe District and Military Hospital, Kigali, evaluated its safety and effectiveness in 55 men.

The study had two phases. In the first, the feasibility of the procedure was evaluated in five individuals. The device was applied and removed in a sterile environment by a physician. In the second phase, the remaining 50 patients were circumcised using PrePex in a non-sterile environment by a doctor or nurse.

The investigators explained that as the rings employed by PrePex only touch intact, healthy skin there is no need for its application or removal to be performed in a sterile environment.

All five patients enrolled in the feasibility phase of the study were successfully circumcised. No adverse events were reported, and all had completely healed within 28 days of the removal of the device.

Circumcision was also successful in all 50 individuals enrolled in the main phase of the study. The device and foreskin were removed between five and seven days after application, somewhat earlier than in the feasibility phase.

The first 20 patients in this phase of the study had the device applied and removed without any form of pain control. However, because some individuals reported discomfort, the remaining 30 patients were treated with 1 g of paracetamol 30 minutes before each procedure.

“We now believe that ibuprofen administered immediately after placement may be a better means of managing discomfort,” comment the investigators.

Only one adverse event occurred after the removal of the device. This involved swelling and occurred in a patient with urethritis caused by a sexually transmitted infection. The swelling disappeared after two days of therapy with the anti-inflammatory drug ibuprofen.

Removal of the foreskin was accompanied by light oozing in two patients. However, this resolved after ten seconds of applied pressure.

A remnant of dead foreskin tissue remained in place after device removal, but this dropped off spontaneously within one to two weeks.

The physician removing the device and dead foreskin detected a slight odour in several instances, but none of the patients complained about smell.

Complete healing was achieved a median of 21 days after the removal of the device. In two patients, however, healing took up to 42 days.

Application of the device took a mean of 4.3 minutes, and its removal (and that of the dead foreskin tissue) a mean of 3.8 minutes.

“Although most of the procedures were handled by physicians, we noted no differences in procedure time, pain, adverse events, or healing time related to whether procedures were performed by a nurse or a physician,” write the authors. “Further study is warranted to document the feasibility of entrusting the procedure to nurses, but these preliminary results are encouraging and potentially important for large-scale male circumcision programs.”

The investigators conclude: “The PrePex device was safe and effective as a means of performing bloodless adult male circumcision that can be performed by non-physician staff without need for anesthesia, suturing, or sterile settings... these promising results could prove to be a significant advance in HIV prevention programs in sub-Saharan Africa.”

Reference

HIV could spread if birth control injections increase, warn scientists

Researchers call for new guidelines for women using family planning services in Aids-hit areas

Research shows that women who use hormonal contraceptives in Aids hit parts of the developing world may double their risk of contracting HIV and passing it to their male partner. Photograph: Vinai Dithajohn/EPA

Campaigns to increase the number of women opting for long-lasting contraceptive injections in Aids-hit parts of the developing world could be helping to spread the epidemic, scientists are warning.

New research shows that women who use hormonal contraceptives may double their risk of contracting HIV and of passing it to their male partner, throwing up a new dilemma for global development.

The authors of the large-scale study, published in the journal Lancet Infectious Diseases, call for urgent guidance to be drawn up and given to women using family planning services in HIV-endemic areas. The study showed particularly that the risk of HIV transmission was raised by the long-lasting injections that are most widely used and most popular in the sub-Saharan regions worst hit by the Aids epidemic.

The results present a significant problem for global health and development. Unwanted pregnancy is a threat to a woman's life and can lead to greater poverty and deprivation for her family. The more children she has, the harder it will be to feed and educate them.

While family planning is still resisted in parts of the developing world, campaigns to promote injectable contraception have met with some success. Many women have sought out the injections that last for months and that they can sometimes get without their husband's knowledge if he refuses permission.

But the study of 3,800 couples shows that there is a risk which has previously been suspected but unconfirmed. The risk was present for those who took the pill too, but it was not statistically significant because most women in the study had opted for injections.

"These findings have important implications for family planning and HIV-1 prevention programmes, especially in settings with high HIV-1 prevalence", said Jared Baeten from the University of Washington, Seattle, one of the study's authors.

"Recommendations regarding contraceptive use, particularly emphasising the importance of dual protection with condoms and the use of non-hormonal and low-dose hormonal methods for women with or at risk for HIV-1, are urgently needed," said lead study author Renee Heffron, also from the University of Washington.

More than 140 million women worldwide use some form of hormonal contraception.

The study group comprised 3,790 couples where one partner had HIV (usually the woman) although the other did not. They were drawn from two existing studies of HIV incidence in seven African countries – Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda and Zimbabwe.

The researchers found that women who did not have HIV were twice as likely to be infected by their partner if they were using hormonal contraception. Those who had HIV themselves were twice as likely to give it to their partner. Tests showed that women with HIV using injectable contraception had raised concentrations of virus inside the cervix. Researchers are unclear why and a larger study specifically designed to look at this issue should be carried out, they say.

Meanwhile women should be told there may be an increased risk of HIV infection if they use hormonal contraception and should be counselled that condoms will give them dual protection.

"Active promotion of DMPA [injectable contraception] in areas with high HIV incidence could be contributing to the HIV epidemic in sub-Saharan Africa, which would be tragic. Conversely, limiting one of the most highly used effective methods of contraception in sub-Saharan Africa would probably contribute to increased maternal mortality and morbidity and more low birth weight babies and orphans—an equally tragic result. The time to provide a more definitive answer to this critical public health question is now; the donor community should support a randomised trial of hormonal contraception and HIV acquisition."

Former Yukos executive diagnosed with HIV months after arrest dies of AIDS complications

By Associated Press, Published: October 3

MOSCOW — A former Yukos executive diagnosed with HIV several months after he was arrested died Monday of complications caused by AIDS, his family said.
The family of Vasily Alexanyan told Dojd television channel that he had died at his home in Moscow at age 39.

Harvard-educated Alexanyan, a vice president at Russia's largest oil company, was arrested in 2006 on embezzlement and money-laundering charges.

He also served as a lawyer for Yukos owner Mikhail Khodorkovsky following his 2003 arrest that was widely seen as Kremlin revenge against Khodorkovsky's political ambitions.

Khodorkovsky is still serving a 13-year sentence on embezzlement and money-laundering charges.

Following the diagnosis, Alexanyan contracted tuberculosis and went nearly blind before his release on bail in 2008.

Khodorkovsky, Western governments and politicians have described the Russian government's treatment of Alexanyan in prison and hospital as "inhumane."

Alexanyan's lawyers have said he was handcuffed to his bed while in the prison hospital, where his legal team and family were denied access to him.

Charges against Alexanyan were dropped in June 2010.

Yukos, once Russia's largest oil producer, was broken up and sold off in auctions ordered by the state to pay off billions of dollars in alleged back taxes.

Fighting a Cancer with Vinegar and Ingenuity


Thailand has gone further than any other nation in adopting a simple, brief and inexpensive technique for preventing cervical cancer. Endorsed last year by the World Health Organization, "VIA/cryo" involves brushing vinegar on a woman's cervix, which makes precancerous spots turn white. A nurse can immediately freeze the white spot off with a metal probe cooled by a carbon dioxide tank available from any Coca-Cola bottler.

Since Thailand's first VIA/cryo pilot trial 11 years ago, not a single one of that trial's 6,000 female participants has developed full-blown cancer. The technique is now routine in 29 of Thailand's 75 provinces.

VIA/cryo—or visual inspection with acetic acid (vinegar) followed, if needed, by cryotherapy—reveals pre-tumors more accurately than a typical Pap smear. Freezing is about 90 percent effective, with the main side effect of a burning sensation that fades in a day or two. The procedure's higher false-positivity rate means some women will get the therapy unnecessarily, however.

"Some doctors resist" VIA/cryo, said Dr. Wachara Eamratsameekool, a gynecologist at the rural Roi Et Hospital who helped pioneer the procedure. "They call it 'poor care for poor people.' This is a misunderstanding. It's the most effective use of our resources."

With its more than 100,000 nurses, who are largely in charge at a network of rural clinics, Thailand seems ideal for VIA/cryo. The screenings are offered free at public clinics, and 500,000 of the 8 million targeted women ages 30-44 have been screened at least once.

Screening twice during her 30s cuts a woman's risk of developing cervical cancer by 65 percent, according to studies by the Alliance for Cervical Cancer Prevention, an international coalition supported by the Bill & Melinda Gates Foundation.

Use Of Injectable Hormone Contraceptive May Double Risk Of Contracting, Transmitting HIV, Study Shows

"The most popular contraceptive for women in eastern and southern Africa, a hormone shot given every three months, appears to double the risk the women will become infected with HIV," according to a study involving 3,800 sero-discordant couples in Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda and Zambia, the New York Times reports. The study, led by researchers at the University of Washington and published Monday in the journal Lancet Infectious Diseases, also found that when the contraceptive was "used by HIV-positive women, their male partners are twice as likely to become infected than if the women had used no contraception," the newspaper writes. In addition, the study "found that oral contraceptives appeared to increase risk of HIV infection and transmission, but the number of pill users in the study was too small to be considered statistically significant, the authors said," according to the New York Times.

"The researchers recorded condom use, essentially excluding the possibility that increased infection occurred because couples using contraceptives were less likely to use condoms," the New York Times notes, adding that "the evidence suggests that the injectable contraceptive has biological properties that
may make women and men more vulnerable to HIV infection." Data from the same study published separately "showed that pregnancy also doubled the risk of women's contracting HIV and of infected women's transmitting it to men," which "may partly be due to increased unprotected sex, but could also relate to hormones, researchers said," the newspaper writes (Belluck, 10/3).

"The results present a significant problem for global health and development," the Guardian writes, adding, "Unwanted pregnancy is a threat to a woman's life and can lead to greater poverty and deprivation for her family" (Boseley, 10/3). "The research, first presented in July in Rome at the meeting of the International AIDS Society, emphasizes the need for couples to use condoms in addition to other forms of contraception in order to prevent pregnancy and HIV," said lead study author Renee Heffron, an epidemiology doctoral student working with the International Clinical Research Center at UW," according to a University of Washington press release (10/3).

In an accompanying commentary, Charles Morrison and Kavita Nanda of FHI360 called for additional research to "provide a more definitive answer" on how hormonal contraception affects HIV transmission and acquisition, the Guardian notes (10/3). According to the New York Times, "[t]he study, which several experts said added significant heft to previous research while still having some limitations, has prompted the World Health Organization to convene a meeting in January to consider if evidence is now strong enough to advise women that the method may increase their risk of getting or transmitting HIV" (10/3).

Cambodia Reports 12,392 Cases Of Dengue Fever, 54 Child Deaths Since January
Cambodia's director of dengue control at the Ministry of Health, Ngan Chantha, said on Monday that from January to September of this year, 12,392 cases of dengue fever had been reported and 54 children have died of the disease, Xinhua reports. In all of 2010, 5,497 cases of dengue and 37 child deaths from the disease were recorded, according to the news agency. "In Cambodia, the outbreak of dengue fever usually begins at the onset of the rainy season from May to October," Xinhua notes (10/3).

Doctors' Support For MMR Vaccine Vital To Halt Measles Outbreaks In Europe, Health Official Says
"With almost 30,000 cases of measles and eight deaths from the disease recorded in the European Union so far this year, a leading health official is urging doctors to do more to ensure parents have their children vaccinated with" the measles, mumps and rubella (MMR) vaccine, Reuters reports. Marc Sprenger, director of the European Center for Disease Prevention and Control (ECDC), "said MMR vaccine coverage rates across the region are currently around 90 percent, leaving significant groups such as children or young adults unprotected," and that "it was crucial for pediatricians and family doctors to give balanced, evidence-based information to help parents decide on vaccinations," Reuters writes.

Some "parents' refusal to have their children vaccinated because of fears of links to autism have caused a rise in measles cases in the United States and Europe in recent years," the news agency notes, adding that "France, Spain, Germany and Switzerland have experienced major measles outbreaks this year, each of them recording thousands of cases" (Kelland, 9/30).

Address Water And Sanitation In Urban Slums To Curb Spread Of Diarrheal Disease
A lack of water and poor sanitation, a result of rapid urbanization being experienced in big cities and small towns throughout the developing world, urgently need tackling in order to curb the resulting spread of diarrheal disease "in what the U.N. terms 'informal settlements'—slums, as they are more commonly known," Timeyin Uwejamomere, senior policy analyst for urban water and sanitation services at WaterAid, writes in this post in the Guardian's "Poverty Matters Blog."

"To me, it is clear: water and sanitation are the most important and essential areas in which we can invest in our booming cities. Such investment improves the lives of the very poorest and has a transformative effect on the national economy and individual wealth," he writes, adding, "A lack of basic toilets and waste management is a severe public health hazard, especially in a dense urban environment where diseases like cholera can spread like wildfire. It is a shocking fact that, in sub-Saharan Africa, more children die from diarrheal diseases caused by a lack of sanitation and safe water than they do from measles, HIV and AIDS, and malaria combined" (10/3).
University of Texas Health Science Center: Alzheimer’s might be transmissible in similar way as infectious prion diseases

HOUSTON—The brain damage that characterizes Alzheimer's disease may originate in a form similar to that of infectious prion diseases such as bovine spongiform encephalopathy (mad cow) and Creutzfeldt-Jakob, according to newly published research by The University of Texas Health Science Center at Houston (UTHealth).

“Our findings open the possibility that some of the sporadic Alzheimer's cases may arise from an infectious process, which occurs with other neurological diseases such as mad cow and its human form, Creutzfeldt-Jakob disease,” said Claudio Soto, Ph.D., professor of neurology at The University of Texas Medical School at Houston, part of UTHealth. “The underlying mechanism of Alzheimer's disease is very similar to the prion diseases. It involves a normal protein that becomes misshapen and is able to spread by transforming good proteins to bad ones. The bad proteins accumulate in the brain, forming plaque deposits that are believed to kill neuron cells in Alzheimer’s.”

The results showing a potentially infectious spreading of Alzheimer's disease in animal models were published in the Oct. 4, 2011 online issue of Molecular Psychiatry, part of the Nature Publishing Group. The research was funded by The George P. and Cynthia W. Mitchell Center for Research in Alzheimer’s Disease and Related Brain Disorders at UTHealth.

Alzheimer’s disease is a form of progressive dementia that affects memory, thinking and behavior. Of the estimated 5.4 million cases of Alzheimer's in the United States, 90 percent are sporadic. The plaques caused by misshapen aggregates of beta amyloid protein, along with twisted fibers of the protein tau, are the two major hallmarks associated with the disease. Alzheimer's is the sixth leading cause of death in the United States, according to the Alzheimer’s Association.

Researchers injected the brain tissue of a confirmed Alzheimer's patient into mice and compared the results to those from injected tissue of a control without the disease. None of the mice injected with the control showed signs of Alzheimer's, whereas all of those injected with Alzheimer's brain extracts developed plaques and other brain alterations typical of the disease.

"We took a normal mouse model that spontaneously does not develop any brain damage and injected a small amount of Alzheimer's human brain tissue into the animal's brain," said Soto, who is director of the Mitchell Center. "The mouse developed Alzheimer's over time and it spread to other portions of the brain. We are currently working on whether disease transmission can happen in real life under more natural routes of exposure."

Earlier Male Circumcision May Help to Slow Rates of HIV, HPV Transmission in South Africa

ScienceDaily (Oct. 6, 2011) — According to Anna R. Giuliano, Ph.D., program leader in cancer epidemiology at Moffitt Cancer Center in Tampa, Fla., and colleagues in the Netherlands, earlier circumcision of males in South Africa may be a positive step in slowing the spread of both HIV and the human papillomavirus (HPV). Their commentary and data were published in a recent issue of the British medical journal The Lancet Infectious Diseases (Vol. 11) 581-582.

"Countries with high incidences of HIV also have high incidences of cancer-related HPV," said Giuliano. "This is especially true in South Africa."

Commenting on a study related to circumcision and HIV and HPV transmission, Giuliano and her colleagues note that studies have shown that circumcision of HIV-infected men does not reduce HPV transmission to their female partners. Many factors may account for this lack of efficacy. However, Giuliano and colleagues suggest that the high prevalence of HPV among the HIV-infected men (73 percent in the intervention group and 69 percent in the control group) and the high prevalence of HIV among the female partners of greater than 60 percent, relates to the lack of efficacy of male circumcision. In that study, it was pointed out that the high and sustained prevalence of HPV among the HIV-infected individuals is "likely to overwhelm any preventative effect of circumcision."

"Male circumcision is important for reduction of not only HIV infection but also HPV infection in HIV-negative men and their female partners," said Giuliano. "However, its efficacy seems limited to HIV-negative men. These results suggest the need for early circumcision to achieve maximum effectiveness in populations with a high incidence of HIV and cervical cancer."

For maximum reductions in HIV and HPV infections and related diseases in women, such as cervical cancer, the researchers recommend that both circumcision and HPV vaccination of the male population should be delivered prior to sexual debut.
Partner Notification of Sexually Transmitted Diseases: Practices and Preferences

*Sexually Transmitted Diseases Vol. 38; No. 9: P. 821-827 (09..2011)

Priya R. Gursahaney; Kwonho Jeong; Bruce W. Dixon; Harold C. Wiesenfeld

Noting that timely notification and treatment of sex partners exposed to an STD “is essential to reduce re-infection and transmission,” the authors undertook the current study to determine factors associated with patient-initiated partner notification and preferences for standard partner referral versus expedited partner therapy (EPT).

A baseline survey was administered to patients diagnosed in the previous year with gonorrhea, chlamydia, trichomoniasis or nongonococcal urethritis. The survey collected information about demographics, sexual history, and partner treatment preferences (standard partner referral vs. EPT). Participants identified up to four sex partners in the past two months, and they answered questions about relationship characteristics, quality, and notification self-efficacy. At follow-up, patients with a current STD were asked whether they had notified their sex partners. Associations between predictor variables and partner notification were evaluated using generalized estimating equations.

A total of 201 subjects were enrolled; 157 had a current STD diagnosis; and they identified 289 sex partners. The rate of successful partner notification was 77.3 percent (157/203 sex partners). Partner notification was increased if the patient was in a long-term relationship with the partner (odds ratio: 3.07; 95 percent confidence interval: 1.43, 6.58); considered the partner to be his/her main partner (odds ratio: 2.53; 95 percent CI: 1.43, 6.58); or had increased notification self-efficacy.

“Overall, participants did not prefer EPT over standard referral; however, females, those with higher education levels, and those with a prior STD preferred EPT,” the authors reported. “Patient-initiated partner referral is more successful in patients with increased self-efficacy who have stronger interpersonal relationships with their sex partners.”

**MSF Calls On Brazilian Government To Step Up Production Of Only Drug For Chagas Disease**

Medecins Sans Frontieres (MSF) has called on the Brazilian government "to ensure its state-owned drug company steps up production of the only drug for Chagas disease, which affects 10 million people in Latin America," Guardian Health Editor Sarah Boseley writes in her "Global Health Blog" (10/6). "Thousands of people with Chagas disease will go untreated in coming months due to a shortage of benznidazole, the first-line drug used in most endemic countries," according to a MSF press release and a related article published by the organization. According to the press release, MSF has stopped diagnosing Chagas in Paraguay and has suspended new projects in endemic areas of Bolivia due to the shortage (10/5).

"There is only one pharmaceutical company in the world making benznidazole and only one supplier of the active ingredient—and they are in Brazil," where the ministry of health "effectively took over responsibility for the production of this drug from the Big Pharma company, the Swiss firm Roche, that no longer found it profitable to make," the blog writes. "But the state-owned pharmaceutical company Lafep and the private chemical company Nortec Quimica have not managed to get sufficient quantities of the drug rolling off the production line—and demand is increasing, because adults are now being treated as well as children," according to the blog (10/6).

**Experts Take Study On Contraceptive Use, HIV Risk Seriously But Warn About Drawing Conclusions Prematurely Because Of Study's 'Methodological Weaknesses'**

In this post in RH Reality Check, Jodi Jacobson, editor-in-chief of the blog, responds to an article published in the New York Times on Tuesday regarding a study suggesting that "HIV-negative women using injectable contraception might face a two-fold risk of acquiring HIV from their infected partners, and that HIV-positive women using injectable contraceptives may be twice as likely to pass the virus on to their uninfected partners." She continues, "Public health and women's rights experts are taking the study very seriously but also caution against drawing conclusions from the NYT story in part because it overstated or misrepresented some of the study's findings while neglecting to mention several potential weaknesses." Jacobson urges the public health community to examine methodological weaknesses of the
study, weigh the evidence presented and balance the risks of any policy or programmatic changes resulting from the study prior to taking action (10/5).

Caitlin Gerdts and Divya Vohra, staff epidemiologists at the Bixby Center for Population, Health & Sustainability at the University of California at Berkeley, also comment on the study in this Daily Beast opinion piece, stating, "The current study suggests that this is a link worth investigating—but in a thorough, careful, and rigorous manner," noting several methodological flaws in the study and the lack of scientific consensus on whether hormonal contraceptives are linked to "higher susceptibility to HIV transmission" (10/6).

Cuts To U.S. Military's HIV Research Program Threaten HIV Vaccine Progress

Fred Sawe, deputy director of the Kenya Medical Research Institute/Walter Reed Project HIV Program in Kericho, Kenya, and Mitchell Warren, executive director of AVAC: Global Advocacy for HIV Prevention, report in Global Health Magazine that "[t]he Department of the Army is set to slash 73 percent of the U.S. Military HIV Research Program’s (MHRP) Army research budget for FY13 through FY17," a move they write is a threat to HIV vaccine progress. They outline recent advancements in HIV vaccine research and recap the U.S. military’s contribution to this research, concluding, "If MHRP funding is drastically cut in the coming years as proposed, it will set back leading scientific research on a course to finding a vaccine, the best weapon against HIV. The Pentagon needs to capitalize on its success, and move forward with its sister agencies, to meet and defeat the national and global threat of HIV" (10/6).

Distinct AIDS viruses found in cerebrospinal fluid of people with HIV dementia

CHAPEL HILL, N.C.—When the virus that causes AIDS infects the central nervous system, it can lead to the development of a severe neurological disease called HIV-associated dementia (HAD). The advent of highly active antiretroviral therapy, or HAART, has helped reduce HAD. But some studies show that HAART may not offer complete protection from less severe HIV-associated neurological problems, nor might it always help to reverse it. As people live longer with AIDS, their risk of developing neurological problems may increase.

New research for the first time may have pinpointed a possible explanation for the problem, one that might also help predict who is at greatest risk for HAD.

Scientists led by researchers from the University of North Carolina at Chapel Hill School of Medicine have discovered that some people diagnosed with HAD have two genetically distinct HIV types in their cerebrospinal fluid (CSF), the clear fluid found in the spaces around and inside the brain and spinal cord. What's more, these variants are not detected in HIV circulating in the blood, and one of them could be present years before the onset of dementia. The detection of these viruses in the CSF is evidence that they are growing in the central nervous system.

In a study published October 6, 2011 in the journal, PloS Pathogens, one of the two HIV variants found in CSF reproduces in immune system T cells, as does the virus growing in the blood. But the other type does not. It infects and replicates in macrophages, another white immune cell that engulf foreign material, including bacteria.

"This is the first time that anyone has demonstrated active replication of HIV virus in a cell type other than T cells," said study senior author Ronald Swanstrom, PhD, professor of biochemistry and biophysics and director of the UNC Center for AIDS Research.

During their own clinical investigations, Swanstrom's current collaborators, neurologists Richard R. Price, MD and Serena Spudich, MD, at the University of California, San Francisco had been collecting blood and CSF samples from patients who had either HIV-associated dementia or other severe neurological defects. Samples were collected with written informed consent from the patients' families. These were the samples used for the current study.

"After the start of therapy, we looked at the rate at which the virus disappeared," Swanstrom said. "We know that HIV in the blood disappears quickly when you go on therapy, and that's because the virus is growing in T cells, which have a very short half-life," the period of time it takes for a substance undergoing decay to decrease by half. Infected T-cells decay by half every one to two days.

But for half of the patients in the new study, HIV growing in the cerebrospinal fluid decayed very slowly, several weeks to one month. "This is evidence the virus is actually being produced by a cell with a longer half-life, and not a T-cell," Swanstrom said.

The researchers also found that the slow-decaying HIV had a particular attraction, or "tropism," to macrophages and were able to infect them.
"Those viruses are known to exist in autopsy brain studies. It has been known for ten years that a subset of HIV-infected patients have slow decay of the virus in the CSF, and it's also been known for a long time that you can find macrophage-tropic virus in the brain," Swanstrom said. "But no one has ever brought the two together in a way that makes sense and could give you a tool to evaluate what's going on in the brain by looking at cerebrospinal fluid."

The study also found HIV-infected macrophages present in a CSF sample two years before the patient was diagnosed with dementia. Swanstrom said this tells us there's information in the CSF that potentially could predict disease progression. "Is it bad to have these viruses around even if you don't get a diagnosis of dementia? And are they potentially causing cognitive damage that can be reversed with HAART?"

To explore these and other questions, Swanstrom and Price of UCSF again will collaborate under a 5-year, $3 million grant from the National Institute of Mental Health to expand the research in HIV patients who don't have dementia and are starting therapy. The new study will look for biomarkers in the CSF in the form of HIV variants or other immune protein information that may predict improvement, stability or decrease in cognitive capacity during therapy.

In the new project, Swanstrom's UNC team will include Joseph J. Eron, MD, professor of medicine and Director of the UNC Center for AIDS Research Clinical Core, Kevin Robertson, PhD, clinical psychologist in the department of neurology, and Angela Kashuba, PharmD, associate professor, Eshelman School of Pharmacy and director, UNC Center for AIDS Research Clinical Pharmacology and Analytical Chemistry Core.

People infected with HIV sometimes delay going on HAART, Swanstrom said. "Our research will help further understand what's going on in the central nervous system of patients who are still alive and in tissue that's accessible in the clinical setting, i.e. CSF. If these individuals knew there was an AIDS virus replicating independently in their CNS, it might affect their decision when to start treatment with HAART."

### Biologists Find 'Surprising' Number of Unknown Viruses in Sewage

ScienceDaily (Oct. 6, 2011) — Though viruses are the most abundant life form on Earth, our knowledge of the viral universe is limited to a tiny fraction of the viruses that likely exist. In a paper published in the online journal mBio, researchers from the University of Pittsburgh, Washington University in St. Louis, and the University of Barcelona found that raw sewage is home to thousands of novel, undiscovered viruses, some of which could relate to human health.

There are roughly 1.8 million species of organisms on our planet, and each one is host to untold numbers of unique viruses, but only about 3,000 have been identified to date. To explore this diversity and to better characterize the unknown viruses, Professor James Pipas, Distinguished Professor of Biological Sciences Roger Hendrix, and Assistant Professor Michael Grabe, all of the Department of Biological Sciences in Pitt's Kenneth P. Dietrich School of Arts and Sciences, are developing new techniques to look for novel viruses in unique places around the world.

With coauthors David Wang and Guoyan Zhao of Washington University in St. Louis and Rosina Girones of the University of Barcelona, the team searched for the genetic signatures of viruses present in raw sewage from North America, Europe, and Africa.

In the paper, titled "Raw Sewage Harbors Diverse Viral Populations," the researchers report detecting signatures from 234 known viruses that represent 26 different families of viruses. This makes raw sewage home to the most diverse array of viruses yet found.

"What was surprising was that the vast majority of viruses we found were viruses that had not been detected or described before," says Hendrix.

The viruses that were already known included human pathogens like Human papillomavirus and norovirus, which causes diarrhea. Also present were several viruses belonging to those familiar denizens of sewers everywhere: rodents and cockroaches. Bacteria are also present in sewage, so it was not surprising that the viruses that prey on bacteria dominated the known genetic signatures. Finally, a large number of the known viruses found in raw sewage came from plants, probably owing to the fact that humans eat plants, and plant viruses outnumber other types of viruses in human stool.

This study was also the first attempt to look at all the viruses in the population. Other studies have focused on bacteria, or certain types of viruses. The researchers also developed new computational tools to analyze this data. This approach, called metagenomics, had been done before, but not with raw sewage.

The main application of this new technology, says Hendrix, will be to discover new viruses and to study gene exchange among viruses. "The big question we're interested in is, 'Where do emerging viruses
come from?" he says. The team's hypothesis is that new viruses emerge, in large part, through gene exchange. But before research on gene exchange can begin in earnest, large numbers of viruses must be studied, the researchers say.

"First you have to see the forest before you can pick out a particular tree to work on," says Pipas. "If gene exchange is occurring among viruses, then we want to know where those genes are coming from, and if we only know about a small percentage of the viruses that exist, then we're missing most of the forest."

Journal Reference:


Africa: UK to Reduce Aid to Anti-Gay Regimes
Joseph Ngugi
9 October 2011

London — African countries which persecute gays will have their aid cut, International Development Secretary Andrew Mitchell has said.

Mr Michael was quoted by the Britain's Mail on Sunday saying that already his country has cut aid to Malawi by £19million after two gay men were sentenced to 14 years hard labour.

Mr Mitchell, one of Mr Cameron's closest allies, is also threatening to impose further aid 'fines' against Uganda and Ghana for hardline anti-gay and lesbian measures.

The policy was disclosed after Mr Cameron defended his decision to legalise gay weddings when he addressed last week's Conservative Party Conference.

It also comes at a time when the divorce of Kenya gay couple in London, Charles Ng'ang'a Wacera and his civil partner, Daniel Chege Gichia were said to be seeking divorce, two years after their internationally debated wedding.

Mr Wacera had told the Nation in an interview last week that the reason why his marriage to Gichia broke down was a campaign of negative publicity by media houses back home in Kenya and in social forums.

The cut in aid to Malawi came after two gay men were convicted last year under the country's rigidly imposed ban on homosexuality.

Pop stars Elton John and Madonna joined an international outcry when Tiwonge Chimbalanga, 26, and Steven Monjeza, 20, received a 14-year sentence for getting engaged.

But a Judge in Malawi was quoted saying in his judgement: "Malawi is not ready to see its sons getting married to its sons."

The Mail reported that Uganda also faced the threat of an aid 'fine' by the UK unless it abandons plans to extend the death penalty to homosexuality.

Three weeks ago, the newspaper said, Mr Mitchell protested to Uganda's President Yoweri Museveni, who has claimed 'European homosexuals are recruiting in Africa' and who believes gay relationships are 'against God's will'.

Uganda is due to receive £70 million from British taxpayers in 2011.

"Again during a visit to Ghana earlier this year, Stephen O'Brien—Mr Mitchell's deputy—told President John Evans Atta Mills that Britain would cut its aid unless he stopped persecuting gays," The Mail claimed.

However, the threats to cut the aid to Ghana appeared to have little effect. Even though Ghana gets £36million a year from the UK, her President has vowed to 'institute measures to check the menace of homosexuality and lesbianism.

And one of his regional ministers called for the 'immediate arrest of all homosexuals'.

A spokesman for Mr Mitchell said: "The Government is committed to combating violence and discrimination against lesbian, gay, bisexual and transgender people in all circumstances, in this country and abroad. We take action where we have concerns."

"We now allocate funds every three months, rather than every year, so that we can review a country's performance, for example on human rights, and take swift action when governments fall short. We only provide aid directly to governments when we are satisfied that they share our commitments to reduce poverty and respect human rights."

Cholera Outbreaks Reported In The DRC, Central African Republic

"There has been an increase in the number of cholera cases and deaths in parts of the Democratic Republic of Congo where an outbreak has been ongoing since March, say humanitarian agencies," IRIN
reports. "At least 6,910 cases and 384 deaths had been reported as of 3 October, according to a report by the U.N. Office for the Coordination of Humanitarian Affairs (OCHA), compared with a total of 3,896 cases and some 265 deaths by 20 July 2011," the news service writes.

"People seeking treatment at various points along the river had exacerbated the spread of the disease as far as Kinshasa," according to Laurence Sailly, the Medecins Sans Frontieres (MSF) assistant medical coordinator, IRIN reports. "Campaigns to encourage prevention measures, such as hand-washing after using the toilet, sensitization on symptoms and increasing the number of latrines at the ports were ongoing," the news service writes (10/7). In related news, "A cholera epidemic in the Central African Republic has claimed 16 victims, a health ministry spokesman said Saturday, as another source said it had reached the capital," Agence France-Presse reports, adding, "Two months ago, health authorities warned of the danger of an outbreak due to the presence of cholera in nearby countries" (10/9).

**Rwandan Government, UNFPA Step Up Campaign To End Obstetric Fistula**

The United Nations Population Fund (UNFPA), the World Food Program and Engender Health have partnered with Rwanda's Ministry of Health in "a campaign to treat and end obstetric fistula in women in Rwanda," the New Times/AllAfrica.com reports. Through the campaign, "at least 50 women are expected to be treated by Issa Labou, a urologist from Senegal, assisted by a team of Rwandan physicians during an exercise to be held at Kibogora Hospital, Nyamasheke District, Western Province from 10-21 October," according to Anicet Nzabonimpa, the family planning and HIV integration coordinator in Rwanda's Ministry of Health, the newspaper writes. "We commit to supporting government’s efforts to fully integrate services that are permanent for ongoing, continuous and holistic care of obstetric fistula cases until we entirely end this preventable and treatable condition,' she said," according to the New Times (10/9).

**Experimental vaccine protects monkeys from blinding trachoma**

**NIH-developed vaccine based on live, attenuated Chlamydia bacteria**

An attenuated, or weakened, strain of *Chlamydia trachomatis* bacteria can be used as a vaccine to prevent or reduce the severity of trachoma, the world’s leading cause of infectious blindness, suggest findings from a National Institutes of Health study in monkeys.

"This work is an important milestone in the development of a trachoma vaccine," noted Anthony S. Fauci, M.D., director of the National Institute of Allergy and Infectious Diseases (NIAID) at NIH. "If this approach demonstrates continued success, the implications could be enormous for the tens of millions of people affected by trachoma, a neglected disease of poverty primarily seen in Asia and sub-Saharan Africa."

In their study, published in the *Journal of Experimental Medicine* online, scientists from NIAID, led by Harlan Caldwell, Ph.D., describe how they tested their vaccine concept in a series of experiments. First they infected six cynomolgus macaques with the strain of *C. trachomatis* that they had weakened by removing a small piece of DNA. The scientists observed that the monkeys spontaneously cleared the infection within 14 days with no or minimal signs of ocular disease. The animals then were exposed twice more to the weakened strain at four- and eight-week intervals, but the animals still showed no signs of trachoma despite being infected.

According to Dr. Caldwell, this finding is particularly significant because repeated *C. trachomatis* infections typically lead to more severe eye disease in people. The infected animals did not develop eye disease, and they all mounted robust immune responses.

The same six macaques then were exposed to a highly virulent strain of *C. trachomatis* as were six other macaques in a control group that had not been vaccinated. Three of the macaques in the vaccine group showed no signs of infection or disease, and the three others showed greatly reduced infection compared with monkeys in the control group. All six macaques in the control group became infected and displayed moderate to severe eye disease that persisted for between two and four months.

Macaques are used in trachoma studies because their immune responses closely predict those of humans. The animals in the study were treated with antibiotics after completion of the experiments, and all recovered completely. The NIAID researchers are currently exploring how they can move their vaccine into human clinical trials.

If left untreated, prolonged trachoma infection can cause a person's eyelids to fold inward, so that the eyelashes rub the eyeball and scar the cornea. This can result in impaired vision and sometimes blindness.
Trachoma is treatable with antibiotics, although in many parts of the world people have limited access to treatment. Currently, there is no vaccine for trachoma. Trachoma experts estimate that approximately 1.3 million people are blind from trachoma, 1.8 million people have low vision as a result of the disease, and an estimated 40 million people have active trachoma. Trachoma is most often spread through direct personal contact, shared towels and other cloths, and flies that have come in contact with the eyes or nose of an infected person.

Chlamydia diseases include sexually transmitted infections, which can result in pelvic inflammatory disease that can cause infertility in women, as well as trachoma. According to the NIAID researchers, findings from this study also could lead to the development of a vaccine against sexually transmitted Chlamydia infections. The Centers for Disease Control and Prevention received more than 1.2 million reports of Chlamydia infections in 2009.

**Can antivirulence drugs stop infections without causing resistance?**

Antivirulence drugs disarm pathogens rather than kill them, and although they could be effective in theory, antivirulence drugs have never been tested in humans. A new study to be published in the online journal *mBio®* on Tuesday, October 18 reveals these drugs have the potential to fight infection while avoiding the pitfalls of drug resistance.

Traditional antibiotics aim to kill or stop the growth of pathogens, but antivirulence drugs prevent disease by neutralizing virulence factors, the specific proteins or toxins that a pathogen uses to establish an infection. Scientists have long thought such a strategy could prevent pathogens from developing drug resistance, since antivirulence drugs don’t kill the pathogens that are susceptible and leave a wide opening for the few resistant organisms that may be left. Thus, in theory, antivirulence drugs don’t offer much benefit to the pathogens that get around the drug. However, these ideas have never been tested.

The study coming out this week provides evidence that antivirulence drugs have the potential to suppress resistance if they are applied in the right way. Brett Mellbye and Martin Schuster from Oregon State University carried out laboratory simulations to determine the effect antivirulence drug-resistant strains could have on therapy. They found that in pathogens that rely on cell-to-cell communication and cooperation, resistant strains will not overtake sensitive strains, allowing antivirulence therapies that target social interactions to work even when resistance arises.

"It’s a very important demonstration of the principle that social effects can slow or even halt the spread of resistance to antivirulence drugs," says Sam Brown, of Edinburgh University, Invited Editor on the study. "Their results align with our understanding of social evolution."

Mellbye and Schuster created a microcosm that simulates an infection, says Brown, and they used bacteria that employ quorum sensing, a form of communication that enables the bacteria to time their attack for greatest effect. Quorum sensing is an important target for antivirulence drugs because many bacterial pathogens, including the lung pathogen Pseudomonas aeruginosa, employ quorum sensing to control the manufacture of their virulence factors.

To circumvent the problem of creating a strain that is resistant to an antivirulence drug, Brown says, the authors used surrogates. "It's kind of a role-playing exercise," to test their ideas, he says. "They used bacteria that behave as we expect drug-resistant bacteria might behave." "Sensitive" mimics are bacteria that lack the ability to communicate and cooperate. "Resistant" mimics are actually run-of-the-mill bacteria that retain the ability to "talk" amongst themselves.

The researchers pitted resistant mimics against sensitive mimics to test whether resistant strains can proliferate in an infection. The results showed that sensitive mimics cheat to get ahead: they exploit the resources that the resistant bacteria provide through quorum sensing. This delays the growth of all the bacteria, suggesting that resistance to an antivirulence drug that targets quorum sensing would not spread. The authors say this highlights the potential of antivirulence strategies that target cooperative behaviors and shared virulence factors.

Brown is optimistic but circumspect about the findings. "These results could very well stand, but in the real world resistance could still emerge and we need to be cautious."

"I think these drugs are promising, even if we do anticipate resistance, because they can slow the rate of resistance evolution, much slower than the rate of resistance evolution to traditional antibiotics," says Brown.
HIV: Ancient Gene Found to Control Potent Antibody Response to Retroviruses

ScienceDaily (Oct. 9, 2011) — A researcher at MIT’s Koch Institute for Integrative Cancer research has identified a gene that controls the process by which antibodies gain their ability to combat retroviruses. Edward Browne shows that the gene TLR7 allows the antibody generating B cells to detect the presence of a retrovirus and promotes a process by which antibodies gain strength and potency, called a germinal center reaction. The findings are published in the Open Access journal *PLoS Pathogens* on October 6th.

TLR7 is a member of an ancient family of genes whose distant ancestors can also be found as far back as insects and worms, but these results show that the immune system has co-opted these genes for a new purpose—the generation of antibodies.

Antibodies are a key feature of our ability to fight off disease causing viruses, but for some viruses such as HIV, this response goes horribly wrong. People infected with HIV generate large amounts of apparently useless antibodies that lack to power to hurt the virus. Why this happens during HIV infection, and how to fix the problem is one of the biggest challenges facing researchers in the HIV field.

During the germinal center reaction, antibodies become mutated and undergo selection to allow the strongest antibodies to dominate. Dr. Browne notes that "these results identify TLR7 as an important gene that could be targeted to improve antibody responses in HIV patients. It’s possible that in HIV patients this process could be enhanced or accelerated to speed up the formation of high affinity broadly neutralizing antibodies."

**Journal Reference:**

Scientists Determine Alternative Insecticide Dramatically Reduces Malaria Transmission

ScienceDaily (Oct. 5, 2011) — Indoor spraying with the insecticide bendiocarb has dramatically decreased malaria transmission in many parts of Benin, new evidence that insecticides remain a potent weapon for fighting malaria in Africa despite the rapid rise of resistance to an entire class of mosquito-killing compounds, according to a study published October 5 in the October edition of *The American Journal of Tropical Medicine and Hygiene*.

Scientists with Benin’s Entomologic Research Center in Cotonou evaluated the effects of two applications of bendiocarb in homes throughout the West African country over an eight-month period in 2009. They found that after “indoor residual spraying” or IRS, which involves applying insecticide on walls where mosquitoes are likely to land, none of the 350,000 household members living in the treated homes "received infected bites" from the malaria-carrying mosquito *Anopheles gambiae*.

Moreover, none of the mosquitoes collected from the treated homes tested positive for the Plasmodium *falciparum*—the world’s most deadly malaria parasite. The absence of infected bites and parasites was seen as evidence that malaria transmission had fallen precipitously in an area where mosquitoes have developed resistance to permethrin and other members of a popular class of insecticides known as pyrethroids.

"Our success in drastically reducing malaria transmission by spraying homes with bendiocarb, which is not a pyrethroid, is very important because pyrethroid-resistance is emerging not just in Benin but also in Kenya, Niger, Nigeria, Mali, Cameroon and many other African countries," Gil Germain Padonou, MSc, a medical entomologist, who co-authored the study. "Our results should provide reassurance that despite the rise in pyrethroid resistance, indoor spraying can continue to play a vital role in reducing the incredible burden of malaria across Africa."

The successful lifecycle of the malaria parasite depends on constantly moving from mosquitoes to humans and from humans back to the mosquito. Indoor spraying and bednets disrupt this lifecycle by broadly preventing mosquitoes from an opportunity to feed on infected blood and thus obtain and transmit the malaria parasite. The researchers believe that where there was indoor spraying, malaria transmission likely continued at a very low level difficult to detect. They conclude that it would have required analyzing "thousands of mosquitoes to find any positive for malaria parasites."

While the study did not formally collect data on how the spraying affected malaria illnesses and deaths, Padonou said there are anecdotal reports from doctors in the region of a "significant reduction in malaria cases" in their clinics following the IRS campaign. Virtually all of Benin’s 9.3 million people are at risk of malaria infections. Each year, malaria sickens more than a million people in Benin and kills thousands. Malaria accounts for about a quarter of all hospital admissions in Benin and a third of the deaths in children under five.
Bendiocarb has been deployed in the fight against malaria despite the fact that it has been voluntarily withdrawn from the U.S. market due to safety concerns. The World Health Organization has approved its use—with strict safety protocols—for indoor spraying programs to combat malaria. Padonou said investigators in Benin monitored for both human and environmental exposures and found no evidence of any adverse events.

The indoor spraying campaign in Benin was conducted by the country's National Malaria Control Program, with support from the U.S. through the President's Malaria Initiative. This is part of a broad effort to find alternatives to pyrethroids, the mainstay of public health campaigns against malaria, chiefly through the distribution of insecticide-treated bednets (ITNs) and indoor spraying campaigns. Malaria experts point to wider use of both interventions—coupled with greater access to malaria medicines and diagnostics—as a key reason why malaria deaths in Africa have dropped by more than a third over the last decade, which represents about 1.1 million lives saved.

However, there are fears that insecticide resistance could stall or even reverse this progress. "Insecticide resistance has been lurking for several years now as a spoiler for the incredible success we have seen in fighting malaria, particularly in Africa, where most of the world's malaria deaths occur," said Peter J. Hotez, MD, PhD, president of the American Society of Tropical Medicine and Hygiene. "We need to intensify support for efforts to develop and test new insecticides and seek better strategies for using them, such as rotating among several different compounds that make it harder for mosquitoes to become resistant. Keeping a constant flow of new products and technologies in pipeline requires funding. If we backpedal now on research and development, we could lose not only the chance to eradicate malaria, but there is also the very real potential we could see an uptick in absolutely preventable malaria diseases, especially among children. This would be unacceptable by any metric."

Padonou and his colleagues worked with the Malaria Control Program to evaluate the capacity of both indoor spraying with bendiocarb and much wider use of ITNs (which continue to be treated with pyrethroids) to interrupt malaria transmission.

Indoor spraying was tested in homes in what is known as the plateau region of Benin, which alternates between wet and dry seasons. But in swampy, frequently flooded areas of Benin, there was concern that indoor spraying with any malaria-killing insecticides could produce toxic runoff into local waterways. Therefore, public health officials opted for increased distribution of ITNs as the primary tool for reducing transmission.

The study reports that both indoor spraying and treated bednets demonstrated a capacity to significantly decrease malaria transmission. For the areas that received indoor spraying, infected bites declined by 94 percent overall during the eight-month study, though in some villages scientists believe infected bites stopped altogether. No one living in a treated home received an infected bite. Bites from infectious mosquitoes also declined substantially in areas where there was increased distribution of ITNs, though the drop was about 5 percent less than what was achieved via indoor spraying.

In contrast, in an area of Benin that received neither indoor spraying nor increased access to treated nets, each resident received an average of 120 infected bites over the same period.

"The best way to control malaria would be to use both indoor spraying and treated bednets, at the same time," Padonou said. Bednets protect people from mosquitoes that may first land and "feed" on a human before lighting on a treated surface and indoor spraying kills mosquitoes en masse offering protection even when you are not sleeping. "Such an approach is too expensive for most national malaria programs and should be reserved for areas that have a particularly high level of malaria."

Researchers are now on the lookout for bendiocarb resistance. Padonou said there is early evidence of resistance in a mosquito population in neighboring Burkina Faso, demonstrating a need to develop multiple alternatives to pyrethroids.

**Overweight patients have best gains in CD4 cell count twelve months after starting HIV therapy**

**Michael Carter**
Published: 11 October 2011

Patients who would normally be classified as overweight have the biggest increases in their CD4 cell counts during the first year of HIV therapy, US investigators report in the online edition of *Clinical Infectious Diseases*. Immune restoration after twelve months of antiretroviral therapy was greatest among individuals with a baseline body mass index (BMI) in the range 25 to 29.9 kg/m², which is usually described as overweight.
In contrast, patients who were seriously underweight or obese at the time they initiated HIV therapy had significantly poorer CD4 cell gains.

“These epidemiological findings suggest that a BMI in the range of 25 – 30 kg/m² may be associated with optimal immune reconstitution in the first year of ART [antiretroviral therapy].”

Being obese (a BMI above 30 kg/m²) is a risk factor for metabolic and cardiovascular complications that are being seen with increased frequency in patients with HIV. In the US it is estimated that between a fifth and a third of all HIV-positive patients are obese, a prevalence approaching that seen in the general population.

However, studies conducted before the introduction of effective HIV therapy showed that a higher BMI (click here for the NHS BMI calculator) was associated with a lower risk of disease progression. Little is known about the impact of baseline BMI on immune reconstitution during antiretroviral treatment.

Therefore investigators from Vanderbilt University School of Medicine, Tennessee, undertook a study involving 915 of their patients who started HIV therapy between 1998 and 2008.

Information was available on the patients' BMI at the time they initiated antiretroviral therapy, and the investigators conducted a series of analysis to see if this was associated with twelve-month changes in CD4 cell count. They adjusted their results for factors such as age, race, baseline CD4 cell count, viral load, type of HIV treatment, and the year therapy was initiated.

Approximately three-quarters (78%) of patients were men and their median age was 39 years. The median baseline BMI was 24 kg/m², with 16% of patients having a BMI below 20 kg/m² (underweight) and 15% a BMI above 30 kg/m². Overall, the patients had advanced immune suppression at the time they started HIV therapy, as the median CD4 cell count was just 171 cells/mm³.

Baseline BMI was associated with changes in CD4 cell count after a year of HIV therapy (p = 0.03). However, the relationship was not linear, and a BMI at both extremes was associated with diminished CD4 cell gains. Patients were categorised according to their baseline BMI (20, 25, 30, and 40 kg/m²). Compared to patients with a BMI in the range 25 to 29.9 kg/m², individuals with a BMI below 20 kg/m² gained significantly fewer CD4 cells (-65 cells/mm³ women; -18 cells/mm³ men).

Similarly, obese women and men had lower twelve-month CD4 cell gains than patients who were overweight (-17 and -12 cells/mm³ respectively).

Baseline viral load, non-white race, the year therapy was started (all p < 0.05) and longer duration of infection with HIV (p = 0.03) were also associated with poorer CD4 cell gains.

The investigators took these findings into account, but their analysis still showed a significant relationship between baseline BMI and immune restoration, with optimum increases observed in patients in the overweight range.

Restricting their analysis to patients whose weight remained stable after starting HIV therapy did not affect their findings (p < 0.01).

Subgroup analyses showed that severely underweight patients with a baseline BMI below 18.5 kg/m² were significantly less likely to have a CD4 cell count of 350 of above after a year of HIV therapy than individuals in the BMI 25 to 29.9 kg/m² reference group, as were morbidly obese patients with a BMI above 40 kg/m² (p = 0.05).

“The magnitude of immune reconstitution 12 months after ART initiation increased with rising BMI and seemed to reach a plateau in the range of BMI 25 to 30 kg/m²,” write the investigators. “The relationship between BMI and CD4 lymphocyte count changes persisted and the strength of the association increased when the cohort was limited to those with a less than 10% weight change.”

The investigators were unclear about the reasons underlying their findings. However, they speculate that patients who were under or overweight were “more likely to have other health conditions or physiologic derangements that impair peripheral CD4 lymphocyte repopulation. They also note, “abdominal obesity is associated with increased cellular immune activation in HIV-uninfected individuals.”

Possible limitations of the study include its observational design and sample size. The researchers also note that they lacked data on their patients’ socio-economic circumstances, factors which could affect both weight and overall health. Moreover, the investigators did not undertake DEXA scans to determine the exact body composition of their patients.

Nevertheless, they conclude, “12-month CD4 lymphocyte recovery was greatest among patients commonly classified as overweight, suggesting an appropriate pretreatment BMI range of 25-30 kg/m² may promote optimal immune reconstitution on ART.”
Cell-Penetrating Peptides Like HIV Tat Have Multiple Ways to Enter Cells

Published on Tuesday, 11 October 2011 00:00

Peptides like the HIV virus Tat protein are able to enter cells using multiple mechanisms, according to a recent laboratory study by researchers at the University of California at San Francisco (UCLA). These peptides have the capacity to carry molecules into cells, which could offer a new approach to targeted delivery of drugs or vaccines.

Below is an edited excerpt from a UCLA media story describing the research and its findings.

UCLA Study Shows Cell-Penetrating Peptides for Drug Delivery Act Like a Swiss Army Knife

October 3, 2011—Cell-penetrating peptides, such as the HIV Tat peptide, are able to enter cells using a number of mechanisms, from direct entry to endocytosis, a process by which cells internalize molecules by engulfing them.

Further, these cell-penetrating peptides, or CPPs, can facilitate the cellular transfer of various molecular cargoes, from small chemical molecules to nano-sized particles and large fragments of DNA. Because of this ability, CPPs hold great potential as in vitro and in vivo delivery vehicles for use in research and for the targeted delivery of therapeutics to individual cells.

But exactly how cell-penetrating peptides—and particularly the HIV Tat peptide—accomplish these tasks has so far been a mystery.

"The HIV Tat peptide is special. People discovered that one can attach almost anything to this peptide and it could drag it across the cell," said Gerard Wong, a professor of bioengineering and of chemistry and biochemistry at the UCLA Henry Samueli School of Engineering and Applied Science and the California NanoSystems Institute at UCLA. "So there are obvious beneficial drug-delivery and biotechnology applications."

In a new study published in Proceedings of the National Academy of Science, UCLA Engineering researchers, including Wong and bioengineering professors Timothy Deming and Daniel Kamei, identify how HIV Tat peptides can have multiple interactions with the cell membrane, the actin cytoskeleton and specific cell-surface receptors to produce multiple pathways of translocation under different conditions.

Moreover, because the researchers now understand how cell-penetrating peptides work, they say it is possible to formulate a general recipe for reprogramming normal peptides into CPPs.

"Prior to this, people didn’t really know how it all worked, but we found that the HIV Tat peptide is really kind of like a Swiss Army Knife molecule, in that it can interact very strongly with membranes, as well as with the cytoskeletons of cells," said Wong, the study’s lead author. "The second part wasn’t well appreciated by the field."

In addition to the membrane activity, researchers discovered that the HIV Tat peptide also creates its own binding site out of the membrane. This means the peptide can actually go through the membrane and induce the cytoskeleton directly to have an endocytic event.

"We found that there are two channels of activity," Wong said. "Because of the peculiar sequence of HIV Tat, it’s very good at being able to interact with membranes. Further, with the high-density packing of charged amino acids in the peptide, it can also interact very strongly with the cell’s cytoskeleton, as well as its receptors."

In addition, the researchers noticed that small cargoes can be transferred directly, while cargoes larger than a few nanometers needed to be anchored to the membrane by the Tat peptide.

Deming, who specializes in synthetic methods, prepared the polypeptide samples for use in the experiments. Kamei, an expert in cellular trafficking, performed cell-based endocytosis experiments using inhibitor drugs and confocal microscopy to identify dominant mechanisms of endocytosis.

"This research is exciting because cell-penetrating peptides have been used in the area of drug delivery for some time," Kamei said. "Gaining any additional understanding of these delivery agents will help in future drug-carrier designs."
It is the group's hope that the new understanding gained from their study will be used to engineer new molecules that are more effective in delivering therapeutic agents.

"This collaboration was important because it combined expertise in the areas of synthesis, characterization and cellular trafficking to address a very relevant problem," Kamei said. "I definitely see more opportunity for combining these areas to tackle other problems in the growing field of biomaterials."

10/11/11

Source

**Counterfeit Drugs Risk Lives, Threaten Pharmaceutical Industry In India**

BBC News examines how counterfeit or substandard medicines are threatening India's fast-growing pharmaceutical industry, writing, "Worth over $12 billion, the industry is expected to grow more than four-fold in the coming decade," but fake drugs in the system are risking both the lives of patients and the reputation of drug makers. While the scale of the problem in India is unknown, "[c]ounterfeit drugs are a $200 billion industry worldwide," and "[w]ith manufacturing costs nearly 40 percent cheaper than other countries, the authorities are worried India could become an easy target for counterfeiters," the news service reports. According to BBC, the Indian government "has launched a campaign against counterfeit medicines," and a "committee set up by the Indian Ministry of Health has approved a proposal to put [two-dimensional] barcodes and scratch-off labels on medicines" that will allow users to use mobile technology to quickly confirm whether a medication is real (Kannan, 10/11).

**Russian Foreign Minister Says Country's HIV/AIDS Problem Is Being 'Aggravated' By U.S., NATO Refusal To Eradicate Poppy Crops In Afghanistan**

Speaking on Monday at a conference on communicable diseases in the eastern Europe and Central Asia region, where AIDS is a growing problem, Russian Foreign Minister Sergei Lavrov made Russia's case for poppy crop eradication by U.S. and NATO forces in Afghanistan asserting that the West "is aggravating the HIV/AIDS problem in Russia and the West by refusing to use its forces to destroy opium crops in Afghanistan," Reuters reports. "Afghanistan is the world's biggest producer of poppies used to make opium, the key ingredient in the production of heroin," the news service writes, adding, "Russia is the largest per capita consumer of the drug and faces an HIV/AIDS epidemic that is spreading from dirty needles." "The United States has phased out crop eradication efforts to focus instead on intercepting drugs and hunting production operations and drug lords," Radio Free Europe/Radio Liberty reports, adding that the U.S. "said it made the change because drug crop eradication was putting farmers out of work, sowing resentment against foreign intervention" (10/10).

**Common antibiotic can have serious adverse reactions**

A commonly prescribed antimicrobial – trimethoprim-sulfamethoxazole – that has been used since 1968 can cause serious adverse reactions and physicians need to be aware of these in prescribing, states a review in CMAJ (Canadian Medical Association Journal) (pre-embargo link only) http://www.cmaj.ca/site/embargo/cmaj111152.pdf.

Trimethoprim–sulfamethoxazole is the most commonly prescribed antibiotic for urinary tract infections in Canada, and is used to treat community-acquired methicillin-resistant Staphylococcus aureus (MRSA) and other bacterial infections. The drug, which is low-cost and effective, is used by hundreds of thousands of Canadians each year, with about 4000 prescriptions each week in Ontario alone.

However, it can cause adverse reactions, some that can be life-threatening, as well as kidney effects (hyperkalemia) and hypoglycemia, which are common results of drug interactions.

"Although trimethoprim-sulfamethoxazole has numerous benefits, particularly in the care of patients with HIV and methicillin-resistant S. aureus, it is associated with multiple toxicities," write the authors. "However, all drugs carry adverse effects. When considering other antimicrobials, clinicians should remember that areas of uncertainty remain, particularly with newer agents."

To help physicians to remember the various possible toxic reactions, the authors propose the NOT RISKY acronym as an aid. They also suggest ways to reduce the risk of trimethoprim–sulfamethoxazole, such as using an alternative antibiotic, especially in pregnant women, and monitoring for kidney issues and hypoglycemia in patients on the drug.
"Clinicians should be cognizant of the potential consequences of prescribing trimethoprim–sulfamethoxazole, monitor patients for adverse events during therapy or use an alternate antibiotic when appropriate," the authors conclude.

**Governor Signs Bills Expanding Drug Users' Access to Sterile Syringes**

*Los Angeles Times*, (10.11.2011)  Diana Marcum

Gov. Jerry Brown has signed into law two bills aimed at reducing the spread of hepatitis C and HIV.

SB 41 allows residents to purchase syringes at pharmacies without a prescription. California was one of the few states where such purchases are illegal, save for pilot programs in certain areas. SB 41 was written by Sen. Leland Yee (D-San Francisco).

The second bill, AB 604, permits the state to authorize needle-exchange programs in high-risk areas. This issue is being debated currently in Fresno, which has one of the highest rates of IV drug use in the country. Last month, the Fresno County Board of Supervisors rejected a plan to legalize a long-running NEP, even as county health officials warned that new HIV and hepatitis C infections were rising.

The League of California Cities and some police organizations opposed AB 604, introduced by Assembly member Nancy Skinner (D-Berkeley), over concerns it would take away local control.

Dr. Marc Lasher, who runs a free medical clinic connected to the Fresno NEP, said AB 604 “allows us to do what’s right health-wise for our patients and our community, and we’ll never have to ask permission ever again from the Board of Supervisors.”

Brown pledged in his signing message that he will ask health officials to implement the law in a “constrained way, working closely not only with local health officers and police chiefs, but with neighborhood associations as well.”

**University of Alabama-Birmingham Researchers Say Babies with Herpes Need More Medication**

*Birmingham News*, (10.06.2011)  Hannah Wolfson

Infants surviving neonatal herpes simplex virus disease with central nervous system (CNS) involvement had improved outcomes on six months of oral acyclovir in addition to traditional therapy, a new study shows. About a quarter of women have HSV, and many do not know they are infected.

“These are little babies and they should not have to face such a challenging start to their lives, and if we have a way that we can improve the likelihood of avoiding that, we should work on it,” said lead study author David Kimberlin, president-elect of the Pediatric Infectious Diseases Society. “When it does occur, not only is it devastating for the babies, it can be devastating for the parents.”

The study involved 74 neonates with HSV at 19 hospitals. All the babies received the regular two to three weeks of IV acyclovir. After completing the IV regimen, infants were randomly assigned either to oral acyclovir or placebo, three times daily for six months. Investigators then checked the infants’ mental development when the babies were a year old.

Far more of the babies with CNS involvement who received oral acyclovir, 69 percent, did well on their 1-year neurological tests. Just 33 percent of those on placebo had normal neurological development, whereas 33 percent were severely impaired. Oral acyclovir did not make much difference in neurological testing for babies with skin, eye, and mouth but not CNS involvement, but the drug did reduce the likelihood of skin recurrence.

Further research will focus on diagnosing HSV in pregnant women as well as on evaluating a new drug for use with IV acyclovir, said Kimberlin, who is a UAB pediatrics professor.


**72 Percent of Indian Youth Have Sex Without Protection**

*Xinhua News Agency*, (10.03.2011)

Up to 72 percent of sexually active young people in India do not use protection with new sex partners, according to a survey reported by the Press Trust of India. Eleven international non-governmental organizations conducted the survey in April and May of this year; the respondents were ages 15 to 35. At least 40 percent of the young people reported difficulty accessing contraception; 36 percent said a relative or close friend had had an unplanned pregnancy; and almost one-third had received incorrect information about contraception from friends.
HIV and TB activist Winstone Zulu dead

Keith Alcorn
Published: 12 October 2011

The prominent HIV and TB activist Winstone Zulu has died at the age of 47 in hospital in Lusaka.

Mr Zulu was diagnosed with HIV in 1990 and was the first person in Zambia to make a public statement about his HIV status.

He began to take antiretroviral treatment in 1996 and contracted tuberculosis in 1997. After effective treatment for TB he became one of the first HIV activists to champion the need to address TB. One of 13 children, Winstone Zulu lost four brothers and two sisters-in-law to TB between 1990 and 2003.

“Not only was Winstone Zulu a hero in the fight against AIDS, but he was also a pioneer in bringing AIDS activism to the hitherto barren and civil society free zone of tuberculosis prevention, treatment, and care,” said Mark Harrington, executive director of Treatment Action Group.

“Winstone was lovely, a courageous, insightful, gentle and eloquent activist and a real pioneer of the HIV and TB access movements for Africans in Africa. He was also that rare thing, a heterosexual man who was honest, wise and funny about male sexuality. He didn’t just defy three epidemic diseases (he had polio as well as HIV and TB), he also survived AIDS denialism,” said Gus Cairns of NAM.

Winstone Zulu stopped HIV medication in 2000 after encountering AIDS denialist views that HIV did not cause AIDS.

He resumed treatment in 2002 after a huge decline in his CD4 cell count left him once again seriously ill.

He continued to play a prominent role in AIDS and TB activism and was praised by Nelson Mandela as a pioneer of TB activism at the 2004 World AIDS Conference. In 2006 he was awarded the Stop TB Partnership Kochon prize for his contribution to TB control.

“Winstone Zulu worked tirelessly to change the world, at no small cost to his own health and wellbeing,” said Mark Harrington. “His legacy is a stronger link between HIV and TB activists, but his inimitable calm and passionate voice of reason will be deeply missed.

Winstone Zulu is survived by his wife Vivian and their four children.

Certain mouth bacteria signal pancreatic cancer

Particular types of mouth bacteria, some of which are found in gum disease, are associated with the development of pancreatic cancer, indicates a small study published online in the journal Gut.

The finding opens up the possibility of curbing the progress of one of the most difficult cancers to treat, by altering the balance of bacteria, say the authors. Pancreatic cancer usually spreads very quickly, and only around one in 20 patients is still alive five years after diagnosis.

The authors base their findings on an initial comparison of the bacteria found in the spit of 10 patients with pancreatic cancer, which had not yet spread, and 10 healthy people, matched for age and sex.

They found significant differences between the bacterial colonies in the two groups, with 31 additional species and 25 fewer species in the spit of the cancer patients.

They then checked spit samples from a further 28 pancreatic cancer patients and 28 healthy people to verify their findings.

And they checked tissue samples from 28 patients with chronic inflammation of the pancreas (chronic pancreatitis), which is associated with an increased risk of developing pancreatic cancer. Among six suspicious species, two—Neisseria elongata and Streptococcus mitis—showed up significantly less often in the mouths of the cancer patients than in those of their healthy peers, while levels of another species—Granulicatella adjacens—were significantly higher.

The combination of N Elongata and S mitis accurately differentiated between healthy patients and those with cancer in more than 80% cases.

Furthermore, they found similar differences in the prevalence of S mitis and G adjacens between the chronic pancreatitis samples and the spit of healthy people.

It is as yet unclear whether the presence of particular types of bacteria are a cause or effect of pancreatic cancer, say the authors. But their findings back previous research, which has implicated bacteria in the development of pancreatic diseases.

They go on to suggest that levels of certain bacteria could be used as a non-invasive and credible screen for pancreatic cancer, with the promise of earlier detection for a disease that has no clear symptoms in its early stages.
Potential new drugs plug brain's biological 'vacuum cleaner' and target HIV

In an advance toward eliminating pockets of infection in the brain that help make HIV disease incurable, scientists report the development of new substances that first plug the biological vacuum cleaner that prevents anti-HIV drugs from reaching the brain and then revert to an active drug to treat HIV. They describe the advance, which allows medications to cross the so-called "blood-brain barrier" (BBB) and treat brain diseases, in the *Journal of the American Chemical Society*.

Jean Chmielewski, Christine Hrycyna and colleagues explain that Human Immunodeficiency Virus infection remains incurable because HIV can sneak through the BBB—a network of special blood vessels and cells that protects the brain from many harmful substances—while many of the most powerful anti-viral medications cannot. A pump at the BBB suctions anti-viral medicines away like a biological vacuum cleaner, leaving a reservoir of HIV in the brain. To overcome this hurdle and get rid of the last footholds of HIV, the researchers set out to develop a new group of drugs that can plug up the vacuuming mechanism and then sneak across the BBB to fight HIV.

Their approach involves gluing two anti-HIV drug molecules together with a "tether." This dual drug plugs up the BBB vacuum cleaner and can then sneak across the BBB. Once across, the tether disintegrates, freeing the two drug molecules to kill the virus. "This overall strategy represents a platform technology that may be readily applied to other therapies with limited brain penetration," such as anticancer and anti-schizophrenia drugs, say the researchers.

Researchers Reconstruct Genome of the Black Death; Bacteria Found to Be Ancestor of All Modern Plagues ***

ScienceDaily (Oct. 12, 2011) — An international team—led by researchers at McMaster University and the University of Tubingen in Germany—has sequenced the entire genome of the Black Death, one of the most devastating epidemics in human history.

This marks the first time scientists have been able to draft a reconstructed genome of any ancient pathogen, which will allow researchers to track changes in the pathogen's evolution and virulence over time. This work—currently published online in the journal *Nature*—could lead to a better understanding of modern infectious diseases.

Geneticists Hendrik Poinar and Kirsten Bos of McMaster University and Johannes Krause and Verena Schuenemann of the University of Tubingen collaborated with Brian Golding and David Earn of McMaster University, Hernán A. Burbano and Matthias Meyer of the Max Planck Institute for Evolutionary Anthropology and Sharon DeWitte of the University of South Carolina, among others.

In a separate study published recently, the team described a novel methodological approach to pull out tiny degraded DNA fragments of the causative agent of the Black Death, and showed that a specific variant of the Yersinia pestis bacterium, was responsible for the plague that killed 50 million Europeans between 1347 and 1351.

After this success, the next major step was to attempt to "capture" and sequence the entire genome, explains Poinar, associate professor and director of the McMaster Ancient DNA Centre and an investigator with the Michael G. DeGroote Institute of Infectious Disease Research, also at McMaster University.

"The genomic data show that this bacterial strain, or variant, is the ancestor of all modern plagues we have today worldwide. Every outbreak across the globe today stems from a descendant of the medieval plague," he says. "With a better understanding of the evolution of this deadly pathogen, we are entering a new era of research into infectious disease."

"Using the same methodology, it should now be possible to study the genomes of all sorts of historic pathogens," adds Krause, one of the lead authors of the study. "This will provide us with direct insights into the evolution of human pathogens and historical pandemics."

The direct descendants of the same bubonic plague continue to exist today, killing some 2,000 people each year.

"We found that in 660 years of evolution as a human pathogen, there have been relatively few changes in the genome of the ancient organism, but those changes, however small, may or may not account for the noted increased virulence of the bug that ravaged Europe," says Poinar. "The next step is to determine why this was so deadly."

Major technical advances in DNA recovery and sequencing have dramatically expanded the scope of genetic analysis of ancient specimens, opening new horizons in the understanding of emerging and re-emerging infections.
DeWitte, Bos and Schuenemann analyzed skeletal remains from victims buried in the East Smithfield "plague pits" in London, located under what is now the Royal Mint. By targeting promising specimens—which had been pre-screened for the presence of Y. pestis—from the dental pulp of five bodies, they were able to extract, purify and enrich specifically for the pathogen's DNA, thereby decreasing the background DNA consisting of human, fungal and other non-plague DNA.

Linking the 1349-1350 dates of the skeletal remains to the genomic data allowed the researchers to calculate the age of the ancestor of the Yersinia pestis that caused the medieval plague. This date coalesced sometime between the 12th and 13th centuries, indicating that earlier plagues such as the Justinian plague of the 6th Century—once thought to have been caused by the same pathogen—was likely caused by another, yet to be determined. The Justinian plague spread across the Eastern Roman Empire, killing an estimated 100 million people worldwide.

The research was funded by the Canadian Institutes for Health Research, the Social Sciences and Humanities Research Council, Canada Research Chairs, an Early Researcher Award from the Ontario Government, the Michael G. DeGroote Institute of Infectious Disease Research, the Wenner Gren foundation, and the Medical Faculty at University of Tubingen.

**Journal Reference:**

**Significant Breakthrough in Study of Chlamydia**
ScienceDaily (Oct. 12, 2011) — A breakthrough in the study of chlamydia genetics could open the way to new treatments and a development of a vaccine for this sexually transmitted disease.

For decades research progress has been hampered because scientists have been prevented from fully understanding these bacteria as they have been unable to manipulate the genome of *Chlamydia trachomatis*.

Now researchers in Southampton have made a significant breakthrough in accessing the chlamydial genome and believe it could pave the way for more effective treatment of the disease.

They hope that it could eventually lead to the development of a vaccine for *C. trachomatis* that is the major cause of sexually transmitted infections in the UK.

The infection is part of a 'silent epidemic' as most cases do not show symptoms and are left untreated. It can cause pelvic inflammatory disease and lead to scarring of the Fallopian tubes causing infertility and higher risk of ectopic pregnancy.

The research was carried out at the Molecular Microbiology Group, at the University of Southampton, in conjunction with the Department of Virology, at the Ben Gurion University of the Negev, in Israel.

Professor Ian Clarke, from the University of Southampton, says: "This is a very significant advance in the study of chlamydia and we are proud to be the first people to achieve this.

"Previously people have been unable to study chlamydial genetics and this has created a barrier to the comprehensive study of this disease.

"We, together with our colleagues in Israel, discovered that by treating the chlamydia with calcium ions we were able to introduce a piece of foreign DNA.

"This will open up the field of chlamydia research and will enable a better understanding of chlamydial genetics. It could lead to the development of new approaches to chlamydial vaccines and therapeutic interventions."

To prove that they had accessed the chlamydial genome, the research team inserted the gene for a fluorescent protein into *C. trachomatis* which identified the chlamydial-infected cells by making them glow green.

Their paper detailing the breakthrough in the study of chlamydia is published in the Public Library of Science journal *PLoS Pathogens* and has also been selected as the Editor's Choice for the journal *Science*.

**Journal Reference:**
Peanut Allergy Turned Off by Tricking Immune System: New Approach Makes Allergen Appear Safe and Prevents Life-Threatening Reaction

ScienceDaily (Oct. 12, 2011) — Researchers have turned off a life-threatening allergic response to peanuts by tricking the immune system into thinking the nut proteins aren’t a threat to the body, according to a new preclinical study from Northwestern Medicine. The peanut tolerance was achieved by attaching peanut proteins onto blood cells and reintroducing them to the body—an approach that ultimately may be able to target more than one food allergy at a time.

"We think we’ve found a way to safely and rapidly turn off the allergic response to food allergies," said Paul Bryce, an assistant professor of medicine in the division of allergy-immunology at Northwestern University Feinberg School of Medicine. Bryce and Stephen Miller, professor of microbiology-immunology at Feinberg, are co-senior authors of a paper published in the Journal of Immunology.

It’s the first time this method for creating tolerance in the immune system has been used in allergic diseases. It has previously been used in autoimmune diseases.

The approach also has a second benefit. It creates a more normal, balanced immune system by increasing the number of regulatory T cells, immune cells important for recognizing the peanut proteins as normal.

"T cells come in different 'flavors'," Bryce said. "This method turns off the dangerous Th2 T cell that causes the allergy and expands the good, calming regulatory T cells. We are supposed to be able to eat peanuts. We’ve restored this tolerance to the immune system."

Peanut allergies often cause life-threatening allergic reactions, called anaphylaxis. Each year there are between 15,000 and 30,000 episodes of food-induced anaphylaxis and 100 to 200 related deaths in the United States, according to the National Institutes of Health. There is no safe treatment to protect people from a severe allergic reaction to food.

When an allergic person eats a peanut, the proteins are absorbed through the intestine and can activate a life-threatening, full-body immune response. This includes constriction of the airways, low blood pressure and/or shock and can lead to loss of consciousness and death.

Using a mouse model that mimics a life-threatening peanut allergy (which the Northwestern team developed several years ago), researchers attached peanut proteins onto white blood cells called leukocytes and infused those back into the mice. After two treatments, the mice were fed a peanut extract. They did not have the life-threatening allergic reaction because their immune system now recognized the protein as safe.

"Their immune system saw the peanut protein as perfectly normal because it was already presented on the white blood cells," Bryce said. "Without the treatment, these animals would have gone into anaphylactic shock." Bryce thinks more than one protein can be attached to the surface of the cell and, thus, target multiple food allergies at one time.

In the second part of the study, Northwestern researchers used the same approach with an egg protein, which was to provoke an immune response—similar to an asthma attack—in the lungs. They attached the proteins to white blood cells and infused the cells back into the mice. When the mice inhaled the asthma-provoking egg protein, their lungs didn’t become inflamed.

"This is an exciting new way in which we can regulate specific allergic diseases and may eventually be used in a clinical setting for patients," said Miller, the Judy Gugenheim Research Professor at the Feinberg School.

Miller also has used the same approach in autoimmune diseases. His previous published research has shown the same technique to stop the progression of multiple sclerosis and type 1 diabetes, both autoimmune diseases, in animal models. This approach is currently being tested in multiple sclerosis patients in a phase I/IIa clinical trial.

For autoimmune diseases and allergic airway diseases, Miller also is working with microparticles rather than white cells to induce tolerance, because the microparticles are more easily standardizd for manufacturing.

**Journal Reference:**
Charles B. Smarr, Chia-Lin Hsu, Adam J. Byrne, Stephen D. Miller, J. Bryce. *Antigen-Fixed Leukocytes Tolerize Th2 Responses in Mouse Models of Allergy*. Journal of Immunology, 2011; 187 (10) [link]
New Equation Predicts Molecular Forces in Hydrophobic Interactions

ScienceDaily (Oct. 11, 2011) — The physical model to describe the hydrophobic interactions of molecules has been a mystery that has challenged scientists and engineers since the 19th century. Hydrophobic interactions are central to explaining why oil and water don’t mix, how proteins are structured, and what holds biological membranes together. Chemical engineering researchers at UC Santa Barbara have developed a novel method to study these forces at the atomic level, and have for the first time defined a mathematical equation to measure a substance’s hydrophobic character.

"This discovery represents a breakthrough that is a culmination of decades of research," says Professor Jacob Israelachvili. "The equation is intended to be a tool for scientists to begin quantifying and predicting molecular and surface forces between organic substances in water."

Using a light-responsive surfactant—a soap-like molecule related to fats and lipids—the researchers developed an innovative technique to measure or change the forces between layers of the molecule in water by using beams of UV or visible light. The result is a general equation that applies to even more complicated systems, such as cellular membranes or proteins.

"We were fortunate to find the right combination of experimental methods and theory," said Brad Chmelka, UCSB Chemical Engineering professor and co-author of the study. "The keys to our research were using a light-responsive surfactant molecule, a means of measuring these delicate surface forces, and applying knowledge of what to look for."

The highly-sensitive instrument they used to sense these molecular-level hydrophobic forces, called a surface forces apparatus, is a now-standard technique that was originally pioneered by Israelachvili and colleagues in the 1970s.

"In basic chemistry, students learn about van der Waal forces—the weak forces that act between all molecules. That theory was developed more than 100 years ago," explains Professor Israelachvili. "According to the van der Waals theory, however, oil and water shouldn’t separate and surfactants shouldn’t form membranes, but they do. There has been no proven theory to account for these special hydrophobic interactions. Such behaviors are crucial for life as we know it to exist."

Hydrophobic and hydrophilic interactions are central to the disciplines of chemistry, physics, and biology that have fueled modern developments in industries from detergents to pharmaceuticals and new biotechnologies. The new equation is expected to impact applications in water filtration, membrane separations, biomedical research, gene therapy methods, biofuel production, and food chemistry.

Virus and disease propagation in the human body are directly linked to hydrophobic properties on a cellular level. One of the problems related to chemotherapy treatments for cancer is being able to direct a drug specifically to cancer cells, instead of the entire body. Israelachvili and his colleagues foresee their discovery having an impact in biomedical research that attempts to understand and treat diseases.

"Cell membranes are complex and discriminating structures, allowing the transmission of various signals into cells and mediating specific interactions with bacteria and viruses," said Jean Chin, Ph.D., who oversees membrane structure grants at the National Institute of General Medical Sciences of the
National Institutes of Health. "This study, by enhancing our understanding of the role played by hydrophobic forces in membrane dynamics, will expand what we know about membrane structure and function, as well as microbial infection pathways."

"Understanding how water and oil-like substances interact is enormously important for explaining the properties and functions of many biological and engineering materials," says Dr. Robert Wellek, Program Director in the Directorate for Engineering at the National Science Foundation. "The UCSB and USC teams have elegantly combined concepts from synthetic chemistry, photophysics, and chemical engineering to unravel and quantify the elusive hydrophobic interaction. NSF is very pleased that its grantees have been able to contribute important fundamental knowledge in this important area."

Details of the research were published this month in the *Proceedings of the National Academy of Sciences*. Their research was made possible by support from the National Science Foundation, the National Institutes of Health, and the Procter & Gamble Company.

"We've known for a long time what we were aiming for. It's a bit like climbing a mountain," said Professor Israelachvili. "The whole thing started at the very bottom. I've been searching for the keys to this interaction for thirty years. We are thrilled with the findings, but it took a lot of steps over carefully chosen paths to get there."

**Journal Reference:**


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**In the absence of antiretrovirals, people living with HIV opt for herbs**

October 13, 2011 Submitted by Mafaranga Country Uganda

In the absence of antiretroviral (ARV) treatment, people living with HIV in Uganda are seeking other ways to delay the onset of AIDS or to treat opportunistic infections, a trend that is worrying health campaigners.

Although many trials of alternative HIV therapies exist, very few meet the scientific standards necessary to support the claims of beneficial effects in the therapies studied.

Denis Kabugho, a resident of Kisuva village in Bundibugyo district, Western Uganda says he resorted to herbs because he could not easily access ARVs. He says the health facilities are far, the services are poor, the lines are long and at times ARVs are not there.

"I have to move a distance of about 40 kilometers to the health center to seek medical services. What hurts me most is that you get there, the nurses are not available, the lines are too long and at the end of it all you go back home, tired, and without being treated," 42-year-old Kabugho says.

Kabugho, who has lived with HIV for the past nine years, says traditional healers usually provide "immediate treatment", whereas clinics may have lengthy waiting lists and tests to determine people who are eligible to start on antiretroviral drugs (ARVs).

However, Grace Businge, who sells herbs in Fort Portal town, says that, although some herbs can be used to boost an HIV positive person's immunity, it is incorrect for people to think they can cure the virus. Businge says most of her HIV positive clients come with complaints of diarrhoea, headaches, loss of appetite and consistent malaria. She discloses that she uses Aloe Vera to treat these symptoms, but was quick to add that the herbs do not cure HIV itself.

"Most people improve after taking a dose of ten liters of Aloe Vera but people should not abandon their treatment because of herbs," she said.

Kabarole district health officer, Dr Richard Mugahi, said many people living with HIV have been deceived to stop taking their medicines, with disastrous consequences.

Dr Mugahi said that many who quit ARVs, or do not take them as prescribed to them by medical workers, get drugs resistance. He added that, by the time they are put back on drugs, they cannot cope and this forces health workers to put the patient on another treatment line of ARVs.

"Adherence is very important in the treatment and management of HIV. Skipping or stopping the drugs put HIV patients in danger of getting more infections and drug resistance," Dr Mugahi said.

"Herbs are likely to be ineffective or can even be harmful. In the absence of good scientific trials, it is impossible to be certain if it works or not. People should avoid it as much as they can," he adds.

Yahaya Maate, one of the people living with HIV, says that one of the reasons why people opt for traditional medicine is because of stigma associated with the virus.
Maate, a resident of Kateebwa in Kabarole district, says he has lived with the HIV for 15 years because he disclosed his status and was helped. Maate does not believe that traditional herbs treat opportunistic diseases associated with the virus. He also disagrees with people taking both the ARVs and herbs.

Maate formed Association of People Living with HIV/AIDS (APHLA) with an aim of sensitizing people on the importance of adherence and protection. The association has over 200 members living with HIV.

He discloses that four of his members died after they abandoned the treatment and resorted to herbs after they were deceived by a witch doctor from the Democratic Republic of Congo who convinced them he had a cure for the virus.

“ARVs do not go well with traditional medicine and if you combine them together it may result into severe side effects and even death,” he said.

Dr Emmanuel Luyirika, the county director of Mild May, described the use of traditional herbs to treat HIV as “a disaster which will lead to multiplication of the virus”. He emphasized that HIV has no cure and no one should stop taking ARVs for traditional medicine, as ARVs have been proven to reduce the virus.

“The consequences of not taking ARVs are fatal and it’s a disaster because when one stops taking it, the virus in the body multiplies, exposing one to death,” he said.

The Country Director of International HIV/AIDS Alliance in Uganda, Leonard Okello, described herbalists and witch doctors who tell people living with HIV that they cure the virus as murderers and called upon the government and the Ministry of Health to apprehend them before they kill many more people.

“This is murder. How can these herbalists and traditional doctors confuse people who are coping well on ARVs, which have been proven to reduce the multiplication of the virus, to stop taking it? We need to take tough action against them before we lose many lives to these unprofessional and selfish individuals,” Okello said.

Working closely on this issue is THETA, a Ugandan NGO dedicated to improving the health of Ugandans by promoting collaboration between traditional and biomedical health systems. It works closely with the Ministry of Health, Uganda Aids Commission, Regional Aids Training Network, universities and several civil society organizations to build and support long term, in-depth relationships between traditional and formal health care systems.

Teens Using Condoms, but Not Always

USA Today, (10.13.2011) Sharon Jayson

The largest-ever federal survey of teens’ sex lives shows high rates of contraceptive use at first intercourse but inconsistent rates thereafter.

The in-person interviews with 4,662 never-married teens ages 15-19 were gathered by CDC’s National Center for Health Statistics between 2006 and 2010. About 43 percent of surveyed girls and 42 percent of boys had had intercourse at least once. The new survey marks the first time there were no racial or ethnic differences in the percentage of teen girls who have had sex, as the proportion of black girls who reported sex decreased from 57 percent in 2002 to 46 percent in 2006-10.

Seventy-eight percent of girls and 85 percent of boys reported using a method of contraception the first time they had sex, with condoms being the most popular. At most recent sex, 86 percent of girls and 93 percent of boys said they had used some form of contraception. However, just 49 percent of girls and 66.5 percent of boys said they used a condom every time they had sex in the past four weeks.

The survey found more girls are using hormonal contraceptive methods not available in earlier years. Use of the pill and injectables had not changed significantly since 2002, 14 percent of girls reported using emergency contraception, 10 the contraceptive patch, and 5 percent the contraceptive ring.

For the 57 percent of girls and 58 percent of boys who said they have never had sex, the most commonly cited reason was “against religion or morals,” given by 41 percent of girls and 31 percent of boys.

Lead author Gladys Martinez, a demographer and statistician, said the survey findings on oral sex will be part of a later data analysis.

A Retrospective Study of HIV Antiretroviral Treatment Persistence in a Commercially Insured Population in the United States

AIDS Care Vol. 23; No. 9: P. 1154-1162, (09..2011)  Timothy Juday; Kristy Grimm; Annette Zoe-Powers; James Willig; Edward Kim

In the current study, the researchers examined factors associated with persistence on initial antiretroviral therapy (the time from ARV treatment initiation to discontinuation) in commercially insured US HIV patients.

The research involved a retrospective analysis of US health insurance claims data from Jan. 1, 2003, to June 30, 2008. It included treatment-naive patients ages 18 to 65 diagnosed with HIV and receiving ARV therapy consisting of at least two individual nucleoside reverse-transcriptase inhibitors (NRTIs) or one fixed-dose combination NRTI, plus at least one nonnucleoside reverse transcriptase inhibitor (NNRTI) or one protease inhibitor (PI), with or without ritonavir. The patients were considered persistent until any component of the regimen was modified or there was a gap in treatment of more than 90 days. Descriptive statistics, Kaplan-Meier survival estimation and Cox proportional hazards regression models were completed.

In all, 2,460 patients (1,388 NNRTI and 1,072 PI) met full inclusion criteria. The mean (SD) time to discontinuation for NNRTI vs. PI-based regimens was 370 (346) vs. 295 (338) days (p<0.001). “Female sex, substance use, low comorbidity score, index year before 2007, geographical region, and taking a lopinavir/ritonavir regimen predicted discontinuation,” the team reported.

“Relative to NNRTI-based regimens, PI-based regimens demonstrated a greater risk of discontinuation (hazard ratio [HR], 1.32; p<0.001),” the authors concluded. “The fixed-dose efavirenz/emtricitabine/tenofovir combination yielded the lowest risk of discontinuation (HR, 0.39; p<0.001). HIV treatment persistence was longer with NNRTI-based regimens than PI-based regimens. The fixed-dose regimen of once-daily efavirenz/emtricitabine/tenofovir had the lowest risk of discontinuation.”

Drug Users to Get Clean Syringes

Post-Standard (Syracuse), (10.12.2011) James T. Mulder

With approval recently granted by the state Health Department, AIDS Community Resources will offer a syringe-exchange program in Syracuse beginning next month. The state will provide ACR $150,000 a year for the SEP, and a one-time $85,000 grant to buy a specialized mobile outreach van.

The van will regularly operate on the east side near East Fayette and Croly streets, and on the west side near Fitch and Dudley streets. Injection drug users (IDUs) can turn in used syringes for sterile ones at the van. In addition, current and former IDUs will walk through targeted neighborhoods doing exchanges from their backpacks.

To obtain syringes, IDUs will have to register with the SEP. They then receive a card to show in case they are stopped by police, since a 2010 state law exempts SEP clients from arrest for possession of syringes containing drug residue. The SEP also will make referrals to detoxification and other health services. “Syringes are a component of a much larger picture,” said Joe Racalto, interim director of the program.

Racalto noted that in addition to street-drug injectors, SEP clients might include high school students who inject steroids, as well as diabetics with inadequate insurance coverage.

The SEP has the strong support of the Onondaga County Health Department, the Syracuse Police Department and Mayor Stephanie Miner.

Syringe exchange is cost-effective, compared with the estimated lifetime cost of $360,000 to care for one person with HIV, said Michael Crinnin, ACR’s executive director. By reducing needle-sharing, the SEP also aims to prevent new hepatitis C infections.

India Faces Nutrition Crisis Despite Growing Prosperity

India's Hindustan Times reports on "a striking contrast between rising economic prosperity and stagnating rates of malnutrition" in Mumbai, where "80,000 children ... are malnourished, according to government data, a statistic that makes Mumbai the most malnourished city in India." The newspaper writes, "Malnourishment in Mumbai could actually be worse than India believes," because estimates are based "on data provided by Integrated Child Development Services (ICDS), a government child-care program that reaches only a quarter of children in the city’s slums."
"Despite three decades of economic growth averaging around six percent ... [n]early half of the world's underweight children are Indians," according to the Times (Bhattacharya, 10/12). "India is still debating a controversial [suggestion] by the head of the planning commission ... that the official poverty line should be lowered to just 32 rupees per person per day for families in urban India and 26 rupees for rural areas (that's $0.65 and $0.48, respectively)," Global Post's "The Rice Bowl" blog reports, adding, "[A]s the story of Mumbai's malnutrition problems suggests, India's increasing wealth disparity is a problem that's as complicated as it is worrying—particularly because government delivery on welfare programs is notoriously bad" (Overdorf, 10/13).

**Malaria Drops From First To Third Cause Of Infant Mortality In Africa, RBM Executive Director Says**

"Over the past three years, malaria passed from first to third cause of infant mortality in Africa, Awa Coll-Seck, executive director of the Roll Back Malaria Partnership [RBM], said Tuesday in Paris," Afrique en ligne reports. "At least 1.5 million children were saved from the disease in recent years, thanks to the successful implementation of national strategies, supported by the international community,' she said," in an interview with [the Pan African News Agency (PANA)], according to the news service.

"According to Coll-Seck, all African countries made headways in combating malaria," Afrique en ligne writes, adding, "In a report released last November, [RBM] indicated that 11 African countries, including Botswana, Equatorial Guinea and Zanzibar, have reduced by 30 percent malaria-related deaths" (10/12).

**Study Finds Vitamin D Is Critical In Human Immune Response To Tuberculosis**

"Vitamin D is needed to activate the immune system's response to tuberculosis (TB)," a finding that "could lead to new treatments for the lung disease," researchers from the University of California in Los Angeles (UCLA) said in a study published Wednesday in the journal Science Translational Medicine, Agence France-Presse reports. "Researchers have long known that vitamin D plays a role in the body's response to TB, but the study ... shows it must be present in adequate levels to trigger the immune response," AFP writes.

"The team notes that vitamin D may help both innate and adaptive immunity, two systems that work synergistically together to fight infections," the Times of India reports (10/13). "This finding could be crucial to efforts to treat the disease in parts of the world like Africa, because people with dark skin ... are more likely to have vitamin D deficiencies," AFP notes (10/12).

**Eating green veggies improves immune defenses**

Researchers reporting online in the journal Cell, a Cell Press publication, on October 13th have found another good reason to eat your green vegetables, although it may or may not win any arguments with kids at the dinner table.

It turns out that green vegetables—from bok choy to broccoli—are the source of a chemical signal that is important to a fully functioning immune system. They do this by ensuring that immune cells in the gut and the skin known as intra-epithelial lymphocytes (IELs) function properly.

"It is still surprising to me," said Marc Veldhoen of The Babraham Institute in Cambridge. "I would have expected cells at the surface would play some role in the interaction with the outside world, but such a clear cut interaction with the diet was unexpected. After feeding otherwise healthy mice a vegetable-poor diet for two to three weeks, I was amazed to see 70 to 80 percent of these protective cells disappeared."

Those protective IELs exist as a network beneath the barrier of epithelial cells covering inner and outer body surfaces, where they are important as a first line of defense and in wound repair. Veldhoen's team now finds that the numbers of IELs depend on levels of a cell-surface protein called the aryl hydrocarbon receptor (AhR), which can be regulated by dietary ingredients found primarily in cruciferous vegetables. Mice lacking this receptor lose control over the microbes living on the intestinal surface, both in terms of their numbers and composition.

Earlier studies suggested that breakdown of cruciferous vegetables can yield a compound that can be converted into a molecule that triggers AhRs. The new work finds that mice fed a synthetic diet lacking this key compound experience a significant reduction in AhR activity and lose IELs. With reduced numbers of these key immune cells, animals showed lower levels of antimicrobial proteins, heightened immune activation and greater susceptibility to injury. When the researchers intentionally damaged the
intestinal surface in animals that didn’t have normal AhR activity, the mice were not as "quick to repair" that damage.

As an immunologist, Veldhoen says he hopes the findings will generate interest in the medical community, noting that some of the characteristics observed in the mice are consistent with those seen in patients with inflammatory bowel disease.

"It’s tempting to extrapolate to humans," he said. "But there are many other factors that might play a role."

For the rest of us, he says, "it’s already a good idea to eat your greens." Still, the results offer a molecular basis for the importance of cruciferous vegetable-derived phyto-nutrients as part of a healthy diet.

**Obstructing MRSA toxin could help bid to beat superbugs**

Researchers have discovered a toxin – SEIX – released by Methicillin-resistant Staphylococcus aureus (MRSA) which leads the body’s immune system to go into overdrive and damage healthy cells. SEIX is made by 95 per cent of *Staphylococcus aureus* bacteria, making it a potential drug target to fight the hospital superbug. Their findings appear October 13th in the Open Access journal *PLoS Pathogens*.

SEIX belongs to a family of toxins known as superantigens that can invoke an extreme immune response. When it is released it triggers an over multiplication of immune cells, which can lead to high fever, toxic shock and potentially fatal lung infections.

The research, carried out by the Universities of Edinburgh, Iowa and Mississippi State, looked at a strain of MRSA known as USA300 that can cause severe infections in otherwise healthy individuals.

Dr. Ross Fitzgerald, from the Roslin Institute at the University of Edinburgh, says "If we can find ways to target this toxin, we can stop it from triggering an over-reaction of the body’s immune system and prevent severe infections."

**Gut bacteria may affect whether a statin drug lowers cholesterol**

DURHAM, N.C.—Statins can be effective at lowering cholesterol, but they have a perplexing tendency to work for some people and not others. Gut bacteria may be the reason.

A research team led by a Duke University scientist has identified three bile acids produced by gut bacteria that were evident in people who responded well to a common cholesterol-lowering drug called simvastatin. The finding, published Oct. 13, 2011, in *PLoS One*, demonstrates how gut bacteria can cause inherent differences in the way people digest, metabolize and benefit from substances such as drugs.

The study represents the intersection of two emerging research interests: An analysis of the intestinal microflora, plus the use of a science called metabolomics, which examines the thousands of biochemical components involved in cellular metabolism and how they affect health.

"This is personalized medicine – the effects of drugs and how we respond," said lead author Rima Kaddurah-Daouk, Ph.D., an associate professor in Duke's Department of Psychiatry and leader of the Pharmacometabolomics Network. "We found that the benefit of statins could be partly related to the type of bacteria that lives in our guts. The reason we respond differently is not only our genetic makeup, but also our gut microbiome."

The researchers gathered data from a subset of participants enrolled in a large, national project called the Cholesterol and Pharmacogenetics (CAP) study, which was led by co-author Ronald M. Krauss, M.D., of Children’s Hospital Oakland Research Institute. In the smaller gut bacteria trial, Kaddurah-Daouk, Krauss and colleagues identified 100 people from the CAP study whose LDL cholesterol fell dramatically as a result of taking simvastatin; 24 who had a fairly good response on the drug; and 24 who showed little benefit.

They then analyzed the blood work from the participants before any had taken the drug, searching for known bile acids and fat-like substances called sterols that are involved in the body’s break-down and use of cholesterol.

**Among the group who had a strong response to the drug, three bile acids appeared to play a role.** The bile acids are produced by certain gut bacteria, which are increasingly understood as factories for chemicals that can contribute to a state of health. **Among the people who responded poorly to the statin, five different bile acids were commonly evident.**

The researchers hypothesize that because bile acids and statins share transporter routes to the liver and intestines – they are basically in competition for a ride—producing more or less of certain bile acids could improve or diminish the drug’s effects.
A blood test that screens for these specific bile acids could provide a way for doctors to determine who would respond to simvastatin and who wouldn't. Additionally, new strategies could be developed to manipulate the gut microbiome using probiotics to spur different gut bacteria, which could then give the drugs a boost.

"We really need to partner with diagnostic and pharmaceutical companies to target drugs for subpopulations," Kaddurah-Daouk said. "It's no doubt that metabolites from bacteria are playing an important role in regulating our systems. We're at a very early stage of understating this relationship, but eventually we could take a quick chemical assay and get a read on where we are metabolically."

'Dark Matter' of the Genome Revealed Through Analysis of 29 Mammals

ScienceDaily (Oct. 12, 2011) — An international team of researchers has discovered the vast majority of the so-called "dark matter" in the human genome, by means of a sweeping comparison of 29 mammalian genomes. The team, led by scientists from the Broad Institute, has pinpointed the parts of the human genome that control when and where genes are turned on. This map is a critical step in interpreting the thousands of genetic changes that have been linked to human disease.

Their findings appear online October 12 in the journal *Nature*.

Early comparison studies of the human and mouse genomes led to the surprising discovery that the regulatory information that controls genes dwarfs the information in the genes themselves. But, these studies were indirect: they could infer the existence of these regulatory sequences, but could find only a small fraction of them. These mysterious sequences have been referred to as the dark matter of the genome, analogous to the unseen matter and energy that make up most of the universe.

This new study enlisted a menagerie of mammals—including rabbit, bat, elephant, and more—to reveal these mysterious genomic elements.

Over the last five years, the Broad Institute, the Genome Institute at Washington University, and the Baylor College of Medicine Human Genome Sequencing Center have sequenced the genomes of 29 placental mammals. The research team compared all of these genomes, 20 of which are first reported in this paper, looking for regions that remained largely unchanged across species.

"With just a few species, we didn't have the power to pinpoint individual regions of regulatory control," said Manolis Kellis, last author of the study and associate professor of computer science at MIT. "This new map reveals almost 3 million previously undetectable elements in non-coding regions that have been carefully preserved across all mammals, and whose disruptions appear to be associated with human disease."

These findings could yield a deeper understanding of disease-focused studies, which look for genetic variants closely tied to disease.

"Most of the genetic variants associated with common diseases occur in non-protein coding regions of the genome. In these regions, it is often difficult to find the causal mutation," said first author Kerstin Lindblad-Toh, scientific director of vertebrate genome biology at the Broad and a professor in comparative genomics at Uppsala University, Sweden. "This catalog will make it easier to decipher the function of disease-related variation in the human genome."

This new map helps pinpoint those mutations that are likely responsible for disease, as they have been preserved across millions of years of evolution, but are commonly disrupted in individuals that suffer from a given disease. Knowing the causal mutations and their likely functions can then help uncover the underlying disease mechanisms and reveal potential drug targets.

The scientists were able to suggest possible functions for more than half of the 360 million DNA letters contained in the conserved elements, revealing the hidden meaning behind the As, Cs, Ts, and Gs. These revealed:

- Almost 4,000 previously undetected exons, or segments of DNA that code for protein
- 10,000 highly conserved elements that may be involved in how proteins are made
- More than 1,000 new families of RNA secondary structures with diverse roles in gene regulation
- 2.7 million predicted targets of transcription factors, proteins that control gene expression

"We can use this treasure trove of new elements to revisit disease association studies, focusing on those that disrupt conserved elements and trying to discern their likely functions," said Kellis. "Using a single genome, the language of DNA seems cryptic. When studied through the lens of evolution, words light up and gain meaning."

The researchers were also able to harness this collection of genomes to look back in time, across more than 100 million years of evolution, to uncover the fundamental changes that shaped mammalian
adaptation to different environments and lifestyles. The researchers revealed specific proteins under rapid evolution, including some related to the immune system, taste perception, and cell division. They also uncovered hundreds of protein domains within genes that are evolving rapidly, some of which are related to bone remodeling and retinal functions.

"The comparison of mammalian genomes reveals the regulatory controls that are common across all mammals," said Eric Lander, director of the Broad Institute and the third corresponding author of the paper. "These evolutionary innovations were devised more than 100 million years ago and are still at work in the human population today."

In addition to finding the DNA controls that are common across all mammals, the comparison highlighted areas that have been changing rapidly only in the human and primate genomes. Researchers had previously uncovered two hundred of these regions, some of which are linked to brain and limb development. The expanded list—which now includes more than 1,000 regions—will give scientists new starting points for understanding human evolution.

The comparison of many complete genomes is beginning to offer a clear view of once indiscernible genomic regions, and with additional genomes, that resolution will only increase. "The power of this resource is that it continues to improve with the inclusion of more species," said Lindblad-Toh. "It's a very systematic and unbiased approach that will only become more powerful with the inclusion of additional genomes."

Journal Reference:

Scientists Move Closer to Predicting Who Will and Will Not Fight Off Severe Infections
ScienceDaily (Oct. 12, 2011) — Why are some people prone to severe infections, while others handle them with less difficulty? A new research report appearing online in the FASEB Journal attempts to answer this question by shedding light on the genetic differences that influence our ability to fight off bacterial infections.

In the report, scientists analyzed the diversity (polymorphisms) in the genetic makeup of an immune system mediator called the macrophage migration inhibitory factor, or MIF, which plays an important role in host defenses against infection. By identifying the gene variations in people that influence the likelihood of developing deadly infections, new tools can be developed to help physicians prescribe the best treatment and approach toward conditions ranging from childhood ear infections to post-surgical recoveries.

"We hope that our study will contribute to facilitating the development of novel treatment strategies targeting the mediator MIF in patients with severe infection (i.e., sepsis) or any other diseases in which MIF has been shown to play an important role," said Thierry Calandra, Ph.D., a researcher involved in the work from the Infectious Diseases Service in the Department of Medicine at the Centre Hospitalier Universitaire Vaudois in Lausanne, Switzerland.

To make their discovery, Calandra and colleagues defined the genetic variations of the MIF gene in a group of children with bacterial sepsis and found that a specific variant of the MIF gene was associated with more severe disease and increased mortality. They also analyzed the transmission of genetic variants of the MIF gene from parents to afflicted children. Results from this family study suggested that one specific variant of the MIF gene protects from meningitis during childhood, while another variant is a risk factor for the development of infection. Considering the existence of a link between variations in the MIF gene, MIF expression, and the development of bacterial sepsis in children, this study data may help identify patients who may benefit from future treatment strategies targeting MIF.

"It's a big step towards personalized medicine. Knowing exactly how the body is programmed to fight infection will prove to be so critical to physicians of the future that new medical school graduates won't be able to imagine how their professors managed without it," said Gerald Weissmann, M.D., Editor-in-Chief of the FASEB Journal. "Here's an analogy: ask a college senior to describe daily life in a world without computers."

Journal Reference:
How Black Death Kept Its Genes but Lost Its Killing Power

The newly sequenced genome of the plague-causing bacterium \textit{Yersinia pestis} suggests human adaptations are what have kept this disease in check.

By Katherine Harmon  | Wednesday, October 12, 2011

From the dust of death: From milligrams of biological material trapped in the teeth of Plague victims, researchers were able to create the first draft genome for the \textit{Black Death} bacterium. Here, 1980s cemetery excavations of the victims. Image: Museum of London Archaeology

In five years, Black Death wiped out an estimated 30 to 50 percent of Europe's population. This medieval plague was caused by the bacterium \textit{Yersinia pestis}, which still circulates among humans. Genetic clues as to what might have made it so deadly, however, had remained interred with the tens of millions of victims.

After careful extraction of genetic material from victims’ teeth, a team of researchers has sequenced 99 percent of \textit{the Plague}’s genome—the first whole-genome reconstruction of a disease from skeletal remains. The draft genome is described online October 12 in \textit{Nature}. (\textit{Scientific American} is part of Nature Publishing Group.)

The 660-year-old plague DNA was isolated from four victims, who had been exhumed from London's East Smithfield Cemetery in the 1980s by the Museum of London Archaeology. To get samples from the skeletal remains, physical anthropologist Kristen Bos of McMaster University in Ontario and a colleague found themselves "wiggling the teeth out of the skulls at the Museum of London," she said in a Tuesday press briefing about the new study.

After carefully extracting genetic material from the inner pulp chamber of the teeth (so as not to damage their exteriors), the team created what Bos called a genetic "fishing rod," baited with molecules from modern-day \textit{Y. pestis}. With that as a lure, "we were able to essentially fish out the small preserved fragments of \textit{Yersinia pestis} DNA" and separate it from the stew of human, bacterial and other genetic material that had accumulated during centuries in the soil. (The team described the actual method, which uses high-throughput DNA sequencing and microRNA enrichment, in an August Proceedings of the National Academy of Sciences paper.)

The genome now gives researchers a sort of "fossil" to start to map out the bacterium's phylogenetic tree. They discovered that the Black Death that devastated Europe between 1347 and 1350 was likely close to the common ancestor of all extant \textit{Y. pestis} strains, (which likely arose—from the soil bacterium \textit{Yersinia pseudotuberculosis}—between 1200 and 1340).

If this was "the first big pandemic with disseminated \textit{Yersinia pestis} in humans," as Johannes Krause, of the University of Tübingen's Institute for Archaeological Sciences, asserted at the briefing, then previous plagues, such as the sixth-century \textit{Plague of Justinian}, were either caused by a completely different pathogen or by a strain of \textit{Y. pestis} that proceeded to go completely extinct.

The new family tree can also help researchers examine related groups, such as the types of plagues that currently affect only rodents (such as \textit{Microtus} strains and those that have been found in Chinese marmots)—and what genetic changes might need to occur to allow them to infect humans.

The sequenced strain has some 4.7 million base pairs. When compared with the modern version (based on 17 different genomes), there are just 90 genetic substitutions. That such few genetic changes occurred over the years, Krause said, was "really surprising."

Among these changes, none obviously explains ancient Black Death's virulence, Hendrik Poinar, also of McMaster, said during Tuesday's prepublication briefing. "There's no particular smoking gun."

So if the slight genetic differences in the disease were not responsible for its drastic change, what did make it so deadly in the 14th century that, as Bos described it, "people honestly thought it was the end of the world"?

Much of the mortality might be explained by situational factors, Poinar explained. Cooler climatic conditions and an excess of rain had led to failed crop harvests and widespread hunger, in addition to large numbers of people living in crowded—already pathogen-filled—medieval cities. "You probably had an immunocompromised population, living under very stressful conditions," Pointer said. Add to that a "population being hit by \textit{Y. pestis} maybe for the first time," and "Black Death was the perfect storm."

Humans have also adapted to the disease. The global population has likely built up some immunity from centuries of exposure to the pathogen. And even before the modern era, virulence was likely quelled by cultural adaptations, Krause noted. During the first outbreak, no one knew what kind of disease it was nor how to treat it, he said. During subsequent outbreaks, however, "people had already developed some
kinds of adaptations—they had developed quarantines, they had developed first aid to treat patients with the symptoms."

And in the meantime, we have developed even more sophisticated surveillance and treatment options, Poinar pointed out. So even if a strain of Y. pestis were to acquire a new batch of mutations, it would still likely be no match for contemporary antibiotics. But that doesn’t mean we’re in the clear, he added. With increased global interaction and more climatic changes on the way, "that will, of course, lead to other zoonotic events where viruses or bacteria can transfer from animals or hosts into the human population," Poinar said.

**Gene variant that helps hepatitis C treatment may hinder HIV treatment**

Gus Cairns
Published: 14 October 2011

A common variant in a gene that doubles the chance of hepatitis C treatment working in people coinfected with HIV may also nearly double the risk of death in patients taking antiretroviral therapy.

A study from Poland found that patients with the so-called 'CC' variant of mutation site rs 1979860 of the IL28B gene were 80% more likely to die during follow-up than patients with the other two possible variants, CT and TT (the letters refer to the particular bases, cytosine and thymine, at that point in the DNA molecule).

Interleukin (IL)28B is also called lambda interferon and is one of the family of natural immune modulators and virus-fighting chemicals produced by the body. Synthetic alpha interferon (in its more potent pegylated form) is standard therapy for hepatitis C and lambda interferon has already been found to produce similar results with fewer side effects as hepatitis C treatment.

In 2009 scientists found that patients infected with hepatitis C and not HIV who possessed the CC variant of the IL28B gene were much more likely both to clear hepatitis C from the body and to achieve a sustained viral response (SVR) in hepatitis C treatment. In initial studies, having the gene conferred a sevenfold improvement in treatment response in mono-infected people. The difference was not so dramatic in people co-infected with HIV: they were not more likely to clear their infection, but the CC variant still doubled the likelihood of treatment success, at least in patients with hepatitis C genotypes 1 and 4, the hardest to treat. Tests for the IL28B gene have now been included in some hepatitis C pre-treatment assays.

Researchers from the Pomeranian Medical University in Szczecin, Poland, decided to see if any IL28B variant was associated with responses to HIV therapy anticipating, as presenter Milosz Parczewski told the conference, that the CC variant might have similarly beneficial effects. They found the opposite. The researchers took longitudinal data on mortality in 484 patients, 84% of whom started antiretroviral therapy during the follow-up period (which followed people up to ten years) and did a genotype test on stored blood samples.

They found that 202 (42%) of patients had the CC variant, a figure consistent with other studies, 46% the CT variant and 12% the TT variant. There was no statistically significant association between any patient characteristic and their genotype, though there was a tendency for patients with CC to have had a higher CD4 nadir.

During the follow-up period, there were 84 deaths (approximately 17% of patients), 55 of them due to AIDS-related conditions and 29 not.

There were proportionately more deaths in patients with the CC genotype, with 46 (23%) of patients with the CC variant dying during the follow-up period compared with 38 (13.5%) of patients with CT or TT.

There was no difference at all in the death rate of patients who were not taking antiretrovirals, but the mortality rates started to differ as soon as patients started combination therapy. In univariate analysis, patients on HIV therapy with the CC variant were 1.8 times more likely to die than those with the ST or TT variants, and this was statistically significant (p=0.029).

In multivariate analysis, the only patient characteristics significantly associated with mortality were female sex (women were 64% less likely to die than men) and CC genotype (people with it were 74% more likely to die, p=0.048). In addition people with a baseline CD4 count of less than 100 cells/mm³ were 80% more likely to die, though this just missed statistical significance (p=0.051).

Why might people with IL28B CC be more likely to die? The Polish researchers found that people with the minority TT variant had a slightly lower baseline HIV viral load and higher highest-ever CD4 count but were unable to establish a difference between patients with CC variant and others.
One interesting fact is that despite being associated with higher levels of HIV treatment success, the CC gene variant is also associated with a higher HCV viral load and a higher risk of liver cirrhosis in people that don’t clear infection. This suggests that the kind of lambda interferon you have might modulate inflammatory processes that, as we are familiar with in HIV, cause tissue damage and disease through immune overstimulation. But why, if the Polish study’s findings are replicated, it only makes a difference in patients on antiretroviral therapy remains unexplained.

Reference

Dolutegravir is potent but twice-daily works better
Liz Highleyman
Published: 14 October 2011

The novel integrase inhibitor dolutegravir is among the most potent antiretroviral agents studied to date, but treatment-experienced individuals need to take it twice-daily in order to achieve optimal concentrations, according to findings presented yesterday at the 13th European AIDS Conference (EACS) in Belgrade.

Dolutegravir (formerly S/GSK1349572 or GSK572) is a next generation integrase inhibitor that remains active against HIV that has developed resistance to the sole approved drug in its class, raltegravir (Isentress).

In the original VIKING study (Cohort I), previously treated patients with extensive drug resistance were treated with 50mg once-daily oral dolutegravir as “functional monotherapy” for ten days, then added an optimised background regimen and continued through week 24.

Although viral suppression was good overall, pharmacokinetic modelling suggested better response might be achieved with higher drug exposure, especially for people with a specific unfavourable pattern of raltegravir resistance mutations.

But drug concentrations reached a plateau when researchers tried to administer larger once-daily doses, leading them to instead test 50mg twice-daily administration in a second group of patients (Cohort II). Again, participants received dolutegravir for ten days then added an optimised regimen through week 24.

As presented by Vincent Soriano from Hospital Carlos III in Madrid, this open-label, single-arm trial enrolled 24 participants on failing antiretroviral therapy with pre-existing resistance to raltegravir and any two other antiretroviral classes. They were required to have at least one available fully active drug to add for regimen optimisation.

Most participants (75%) were men and the median age was 47 years. They were generally similar to people in the original Cohort I, except they had less advanced HIV disease and were more likely to be coinfected with hepatitis B or C (about 20%). The median CD4 cell count was about 200 cells/mm³. They had been taking antiretroviral for a median of 15 years and had used a median of 15 different drugs; half were already resistant to the newest available agents.

Participants were divided into two groups based on integrase resistance pattern at baseline; 46% had the Q148 mutation plus at least 1 secondary mutation which significantly reduces susceptibility to dolutegravir whilst 54% had all other mutation patterns combined.

At 24 weeks 75% of participants receiving twice-daily dolutegravir achieved undetectable viral load below 50 copies/mL, compared with just 41% of those who took the drug once-daily in Cohort I. As expected, people who had more available active drugs for optimisation did better (67% undetectable with one active drug, 79% with two).

Six participants were classified as nonresponders: four who never suppressed viral load through week 24, one who did so but then experienced viral rebound, and one protocol violation; there were no discontinuations due to adverse events and no deaths in Cohort II. Dolutegravir was well-tolerated overall, with the most common side-effect being mild diarrhoea.

In a multivariate analysis of Cohort I and Cohort II combined, factors that independently predicted response to dolutegravir at 24 weeks were baseline integrase resistance mutation pattern, availability of other active drugs for optimisation, higher baseline CD4 cell count and dolutegravir concentration in the blood at day 10.

Based on these findings, 50mg twice-daily dolutegravir was chosen for further evaluation in a Phase 3 trial. Soriano said an expanded access program is expected to begin in early 2012.
As raltegravir must also be given twice-daily, this dosing frequency does not put dolutegravir at a disadvantage in an era when people with HIV and their clinicians favour once-daily therapy.

Data from the SPRING-1 study showed that once-daily dolutegravir is adequate for treatment-naive individuals, however, suggesting that this is another drug that will be dosed differently depending on prior treatment history.

Reference

Scripps Research Scientists Reveal Surprising Picture Of How Powerful Antibody Neutralizes HIV
14 Oct 2011

Researchers at The Scripps Research Institute have uncovered the surprising details of how a powerful anti-HIV antibody grabs hold of the virus. The findings, published in Science Express on October 13, 2011, highlight a major vulnerability of HIV and suggest a new target for vaccine development.

"What’s unexpected and unique about this antibody is that it not only attaches to the sugar coating of the virus but also reaches through to grab part of the virus’s envelope protein,” said the report’s co-senior author Dennis Burton, a professor at The Scripps Research Institute and scientific director of the International AIDS Vaccine Initiative’s (IAVI) Neutralizing Antibody Center, based on the Scripps Research La Jolla campus.

"We can now start to think about constructing mimics of these viral structures to use in candidate vaccines,” said co-senior author Ian Wilson, who is Hansen Professor of Structural Biology and member of the Skaggs Institute for Chemical Biology at Scripps Research.

Other institutions in the United States, United Kingdom, Japan, and the Netherlands contributed to the research as part of an ongoing global HIV vaccine development effort.

Getting a Better Grip on HIV

Researchers from the current team recently isolated the new antibody and 16 others from the blood of HIV-infected volunteers, in work they reported online in the journal Nature on August 17, 2011. Since the 1990s, Burton, Wilson, and other researchers have been searching for such "broadly neutralizing" antibodies against HIV antibodies that work against many of the various strains of the fast-mutating virus and by now have found more than a dozen. PGT 128, the antibody described in the new report, can neutralize about 70 percent of globally circulating HIV strains by blocking their ability to infect cells. It also can do so much more potently in other words, in smaller concentrations of antibody molecules than any previously reported broadly neutralizing anti-HIV antibody.

The new report illuminates why PGT 128 is so effective at neutralizing HIV. Using the Wilson lab’s expertise in X-ray crystallography, Robert Pejchal, a research associate in the Wilson lab, determined the structure of PGT 128 joined to its binding site on molecular mockups of the virus, designed in part by Robyn Stanfield and Pejchal in the Wilson group and Bill Schief, now an IAVI principal scientist and associate professor at Scripps Research, and his group. With these structural data, and by experimentally mutating and altering the viral target site, they could see that PGT 128 works in part by binding to glycans on the viral surface.

Thickets of these sugars normally surround HIV’s envelope protein, gp120, largely shielding it from attack by the immune system. Nevertheless, PGT 128 manages to bind to two closely spaced glycans, and at the same time reaches through the rest of the "glycan shield" to take hold of a small part of structure on gp120 known as the V3 loop. This penetration of the glycan shield by PGT 128 was also visualized by electron microscopy with a trimeric form of the gp120/gp41 envelope protein of HIV-1 by Reza Kayat and Andrew Ward of Scripps Research; this revealed that the PGT 128 epitope appears to be readily accessible on the virus.

"Both of these glycans appear in most HIV strains, which helps explain why PGT 128 is so broadly neutralizing," said Katie J. Doores, a research associate in the Burton lab who was one of the report’s lead authors. PGT 128 also engages V3 by its backbone structure, which doesn’t vary as much as other parts of the virus because it is required for infection.

PGT 128’s extreme potency is harder to explain. The antibody binds to gp120 in a way that presumably disrupts its ability to lock onto human cells and infect them. Yet it doesn’t bind to gp120 many times more tightly than other anti-HIV antibodies. The team’s analysis hints that PGT 128 may be extraordinarily potent because it also binds two separate gp120 molecules, thus tying up not one but two cell-infecting structures. Other mechanisms may also be at work.
Toward an AIDS Vaccine
Researchers hope to use the knowledge of these antibodies’ binding sites on HIV to develop vaccines that stimulate a long-term perhaps lifetime protective antibody response against those same vulnerable sites.

"We'll probably need multiple targets on the virus for a successful vaccine, but certainly PGT 128 shows us a very good target," said Burton.

Intriguingly, the basic motif of PGT 128’s target may mark a general vulnerability for HIV. "Other research is also starting to suggest that you can grab onto two glycans and a beta strand and get very potent and broad neutralizing antibodies against HIV," Wilson said.

"Functional Cure" For HIV/AIDS Glimpsed In Small Trial
19 Sep 2011
Researchers testing a potential new gene therapy for HIV/AIDS say they are excited by early results that represent significant progress towards a "functional cure" for the disease. They have presented the data from the phase 1 clinical programs to develop the treatment known as SB-728-T, from Sangamo BioSciences, Inc. of Richmond, California, at the 51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAA), which is being held in Chicago this week, from 17 to 20 September.

Sangamo is a biotech company that specializes in developing technology that switches genes on and off by manipulating a class of transcription factors called zinc finger DNA-binding proteins (ZFPs). They also develop technology that can fine tune or edit gene expression using zinc finger nucleases (ZFNs) that insert, delete or change specific sequences of DNA.

One of the reasons HIV is able to infect cells in the human immune system is because of the CCR5 gene: it codes for a receptor that the virus uses to gain entry.

Sangamo has developed its experimental treatment SB-728-T to modify this facility in both copies of the CCR5 gene (each person has two copies or alleles of a gene, one from each biological parent).

The idea is to modify enough genes in enough cells that the viral load is considerably diminished, thus removing the need to continue with highly active antiretroviral therapy (HAART).

Dr Carl June, Director of Translational Research at the Abramson Family Cancer Research Institute at the University of Pennsylvania School of Medicine is an investigator on the trial:

June told the press that: "The statistically significant relationship between estimated modification of both copies of the CCR5 gene and viral load during the treatment interruption suggests that the next step is to increase the frequency of the modified cells in HIV-infected patients with the ultimate hope that if we do, we will achieve a 'functional cure' and eliminate the need for continued HAART."

The trial involved 10 patients who were on HAART when they joined.

Four weeks after treatment with a single dose of SB-728-T, six of them underwent treatment interruption (TI), where they stopped taking the HAART medication for 12 weeks.

Viral load went down in three of the six patients. In one patient the viral load became practically undetectable, to the point where he was considered "aviremic" at the end of the treatment interruption. This patient already had a naturally mutated copy of the CCR5 gene (so his genes were already half-way to the finishing post as far as this treatment was concerned).

The researchers estimated that the percentage of CCR5 genes (counting both copies) that were switched off (thus denying HIV entry to cells) in this patient was twice that of the other patients (none of whom had already modified copies of the gene when they joined the study).

Dr Ronald Mitsuyasu, Professor of Medicine, David Geffen School of Medicine at University of California Los Angeles (UCLA) is a principal investigator on this part of the trial. He said they were "very encouraged by this early demonstration" of an antiviral effect, and also the "marked improvement" in the overall CD4+ immune T-cell counts of the patients.

"While their viral loads are well controlled on HAART, these subjects experienced incomplete restoration of their T-cell counts. Improvement and preservation of the immune system is of paramount importance in HIV and those seen in this study show an improvement over that seen after several years of HAART," said Mitsuyasu.

Dr Dale Ando, Sangamo's vice president of therapeutic development and chief medical officer said: "SB-728 treatment results in unprecedented improvement in immune system health as measured by increased CD4+ T-cell levels and improved CD4+: CD8+ T-cell ratios, even in subjects that entered the trial with poor CD4+ counts."
Sangamo’s executive vice president of research and development, Geoff Nichol, said they are continuing to “collect valuable data about the parameters essential for optimization of this novel drug candidate”.

The company plans to expands its clinical trials and do confirmatory studies in patients who carry a natural already modified copy of the CCR5 mutation.
"We will also explore other mechanisms to enhance engraftment and maximize the impact of the HIV resistant cells on viral load and the overall immune system of HIV patients," said Nichol.

Sangamo’s statement pointed out that Mitsuyasu and June have no financial ties with the company.

Written by Catharine Paddock PhD
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Dangerous Precedent: HIV-Positive Man Convicted for Infecting His Informed, Consenting Partner ***

Last Friday, Oct. 7, 2011, a court in Minneapolis convicted Daniel James Rick of first-degree assault. His weapon: a disease he carried in his body, HIV.

In 2009, Rick had consensual, unprotected sex with his victim (unnamed). Rick says that before they had sex, he disclosed his HIV status, and the victim chose to engage in unprotected anal sex anyway. The victim later tested positive for the HIV virus, blamed Rick and charged him with assault. After a one-week trial, a jury convicted him of a felony.

In case there's confusion, let’s break that down again: Rick and this guy decided they wanted to have sex. Rick informed this potential sexual partner he was HIV-positive. The potential sexual partner understood that Rick was HIV-positive and agreed to have anal sex without a condom.

Later, Rick’s unnamed sexual partner tests positive for HIV and believes Rick transmitted it to him during their night together. This partner then decides his HIV infection was not the result of poor decision-making; instead, he decides he was the victim of assault. And then, a couple of years later, a jury agrees with him. Now Rick could go to jail for years.

The conviction hinged on a 16-year-old Minnesota statute, 609.2241, which states a person can be prosecuted when transferring a communicable disease through:

1. Sexual penetration with another person without having first informed the other person that one has a communicable disease
2. Transfer of blood, sperm, organs or tissue, except as deemed necessary for medical research, or if disclosed on donor screening forms
3. Sharing of nonsterile syringes or needles for the purpose of injecting drugs

Since the jury believed Rick disclosed his status, they found him innocent of the first clause, but determined they had to convict him because of the second clause, believing it applied to any transfer of sperm, not just transfers in medical settings.

To be clear, Rick is not the picture of sexual function. He has been convicted of raping a 15-year-old boy and has three pending charges of attempted first-degree assault for having sex without disclosing his HIV status.

Still, the implications of this verdict are unsettling, distressing and enraging.

It's unsettling because there are 34 states where the transmission of HIV is considered either assault, assault with a deadly weapon or attempted murder. There is now precedent to convict anyone who is HIV-positive and transmits the disease to a consenting partner—the entire positive community suddenly is now one condom break or bareback session away from being a criminal.

It’s distressing because this verdict may further stigmatize the disease. Legal scholars have argued this type of verdict may lead to fewer people choosing to be tested for HIV. If a person doesn’t know they are positive, they can claim plausible deniability if one of his or her partners gets infected and presses charges.

It's enraging because the statute listed above wasn’t written in reference to any communicable disease. It was written about HIV. No other transmittable disease results in convictions of assault. If a small child or elderly person dies from the flu, no one is charged with assault. No one is thrown into jail for transmitting HPV to someone who later develops deadly cervical or throat cancer. People are only charged for transmitting HIV. The statute in Minnesota and those like it are based in homophobia and ignorance of the disease.
HIV is no longer seen as a death sentence; instead, treatment advances have made HIV a chronic, manageable disease. This fact is not lost on the current White House. In July 2010 the White House declared, "The continued existence and enforcement of these types of laws [criminalizing HIV infection] run counter to scientific evidence about routes of HIV transmission and may undermine public health goals of promoting HIV screening and treatment."

On Sept. 23, 2011, Congresswoman Barbara Lee (D-Calif.) decided to do something to get rid of these discriminatory laws by introducing a bill, H.R. 3053: The Repeal Existing Policies that Encourage and Allow Legal HIV Discrimination Act, or the REPEAL HIV Discrimination Act. This act calls for the review of all laws, policies and regulations regarding the criminal prosecution of individuals for HIV-related offenses.

This bill could undo the damage caused by Rick's conviction.

The REPEAL HIV Discrimination Act has a long way to go before it becomes a law, and, given the current congressional climate, passage will be difficult. There are things we can all do to ensure it doesn't disappear in a House committee. There are currently 14 co-signers, but it's important to build as much support as possible. Talk to your congressperson today to add their support to this bill. Talk to your senators to create a similar bill. Most importantly, let as many people as possible know that it's important to get rid of these discriminatory laws.

**UK Study Shows How Better HIV Drugs Extend Lives**

*Reuters*, (10.12.2011) Kate Kelland

Life expectancy in UK residents treated for HIV infection grew by over 15 years during 1996-2008, largely due to earlier diagnosis and treatment with better, less toxic drugs, according to a new study.

Researchers analyzed data from the UK Collaborative HIV Cohort Study, focusing on patients age 20 and older who initiated antiretroviral therapy with at least three drugs, at a CD4 count of 350 cells/mm³ or less, during 1996-2008. Of 17,661 eligible patients, 1,248 died during the period. Researchers calculated the additional years that a study patient could expect to live after age 20.

Life expectancy for an HIV patient at age 20 increased from an additional 30 years to almost 46 years between 1996-99 and 2006-08. The average life expectancy for female patients was 10 years higher than for males. At age 20, male HIV patients receiving treatment could expect to live about 40 additional years, and women with HIV 50, compared with 58 and nearly 62 additional years for men and women in the general population. However, "Starting antiretroviral therapy later than guidelines suggest resulted in up to 15 years' loss of life," the authors wrote.

"These results are very reassuring news for current patients and will be used to counsel those recently found to be HIV-positive," said study co-leader Mark Gompels of the North Bristol National Health Service Trust.

"We should expect further improvements for patients starting antiretroviral therapy now with improved modern drugs and new guidelines recommending earlier treatment," said co-leader Margaret May of Bristol University. The complete open-access study, "Impact of Late Diagnosis and Treatment on Life Expectancy in People with HIV-1: UK Collaborative HIV Cohort (UK CHIC) Study," was published in the British Medical Journal (2011;doi:10.1136/bmj.d6016).

**EACS: Do Women with HIV Experience Earlier Menopause?**

Published on Thursday, 13 October 2011 00:00
Written by Liz Highleyman

Premature menopause may be more common among women with HIV, but the difference is primarily driven by women with advanced immune deficiency, according to study results presented at the 13th European AIDS Conference (EACS 2011) this week in Belgrade.

Research over the course of the epidemic has produced conflicting findings about changes in menstruation and menopause among women with HIV, but much of this data came from earlier years when HIV positive people typically developed advanced disease.

Investigators with the DIDI Study looked at prevalence and factors associated with early menopause in HIV positive women. Hormonal changes at menopause increase the risk of co-morbidities including cardiovascular disease and bone loss, they noted as background, which already occur at higher rates among people with HIV.

A total of 352 HIV positive women at 15 infectious diseases clinics in Italy completed anonymous self-administered questionnaires about their overall health status, gynecological health, and mental and
physical health. The researchers compared survey findings, demographics, and clinical characteristics of pre-menopausal and early post-menopausal women.

Participants were under 46 years of age (median 40 years), the age at which perimenopause typically occurs among women in the general population. Early menopause was defined as a full year without menstrual periods, not explained by other causes, in women younger than 46 years.

Participating women had been diagnosed with HIV for a median of 11 years; Most were taking antiretroviral therapy (ART) and about 20% had a prior AIDS diagnosis (CDC stage C). In addition, 18% had a history of illegal drug use and 17% were immigrants.

Results

- 27 women (7.6%) reported early menopause.
- In 9 cases (5.2%), early menopause occurred in women less than 40 years of age.
- Women with early menopause were more to have a history of drug use (25.9% vs 17.2%), but this did not reach statistical significance.
- Women with early menopause had been diagnosed with HIV for a significantly longer time (18 vs 10 years) and were more likely to have AIDS (41.7% vs 17.1%).
- However, nadir (lowest-ever) CD4 count and ART use were similar in the pre-menopausal and post-menopausal groups.
- Women with early menopause reported lower overall, physical, and mental health scores.
- In a multivariate analysis controlling for other factors, early menopause was significantly associated with having AIDS (adjusted odds ratio 3.33, or about 3-fold higher risk).
- There was a trend towards an association between younger menopause and younger age at first menstruation, but this did not reach statistical significance.
- Women who reported early menopause were more likely to receive annual mammograms and DEXA scans to monitor bone loss.

The investigators noted that the prevalence of early menopause in this analysis (7.6%) was comparable to the prevalence in a 2003 Italian general population study (7.1%). However, they added, the present study found a higher rate of premature menopause among women under age 40 (5.2% vs 1.8%, respectively).

"Advanced stage of [HIV] disease represents the main predictor of early menopause," they concluded. "As suggested by good clinical practice, post-menopausal HIV [positive] women more likely undergo annual co-morbidity screening." 10/14/11

Reference

**Indoor Cooking Stoves Kill 2 Million Annually, NIH Study Says**

Pollution from indoor cooking stoves, typically open fires that burn solid fuels such as wood, charcoal or dung, kills two million globally each year, scientists at NIH said in a study published in the journal Science on Thursday, Agence France-Presse reports. Smoke emitted from the stoves, used by three billion people worldwide, "causes pneumonia and chronic lung disease that particularly affects women and children who tend to spend more time in the home while men are outside working," AFP writes, adding that "little public awareness surrounds what the World Health Organization describes as the globe's top environmental killer" (Sheridan, 10/13).

"To help change this, some $150 million to $200 million worth of research needs to be done over the next decade to see that clean cookstoves get into the homes of the women most vulnerable to the hazards of indoor pollution, the scientists wrote," according to Reuters. "The research should include examinations of respiratory, cardiovascular and cancer risks as well as such life-cycle concerns as maternal, neonatal and child health, said Dr. William Martin II of the [NIH], one of the report's authors," the news service writes (Zabarenko, 10/13).

**Limited Research On Sexual Violence Against Men In The DRC Suggests Issue Is 'Largely Ignored'**

IRIN reports on the issue of sexual violence against men as a in the Democratic Republic of the Congo (DRC), writing, "Sexual violence against men, including rape, is under-reported, poorly addressed and has a severe impact on both men and their families, according to a presentation at the annual Sexual Violence and Research Initiative (SVRI), held in Cape Town, South Africa." The news service writes, "The eastern
DRC makes up most of the available research on sexual violence during conflict, according to Claudia Moreno, coordinator of the World Health Organization’s Department of Gender and Women."

"Jocelyn Kelly of the Harvard Humanitarian Initiative at Harvard University, said the term ‘sexual violence’ in DRC had become synonymous with the rape of women by armed groups, leading programs to exclude female and male survivors of abuse and gender-based violence (GBV), and male survivors of conflict-related sexual violence," IRIN writes. The news service highlights the results of two small, qualitative studies that explore the issue of rape against males in the DRC (10/13).

Grenoble, 13 October 2011

**Intruder detected: raise the alarm!***

How a molecular switch activates the anti-viral innate immune response
When a thief breaks into a bank vault, sensors are activated and the alarm is raised. Cells have their own early-warning system for intruders, and scientists at the European Molecular Biology Laboratory (EMBL) in Grenoble, France, have discovered how a particular protein sounds that alarm when it detects invading viruses. The study, published today in Cell, is a key development in our understanding of the innate immune response, shedding light on how cells rapidly respond to a wide range of viruses including influenza, rabies and hepatitis.

To sense invading agents, cells use proteins called pattern recognition receptors, which recognise and bind to molecular signatures carried only by the intruder. This binding causes the receptors to change shape, starting a chain-reaction that ultimately alerts the surrounding cells to the invasion. How these two processes – sensing and signalling – are connected, has until now remained unclear. The EMBL scientists have now discovered the precise structural mechanism by which one of these receptors, RIG-I, converts a change of shape into a signal.

"For a structural biologist this is a classic question: how does ligand binding to a receptor induce signalling?" says Stephen Cusack, who led the work. "We were particularly interested in answering it for RIG-I, as it targets practically all RNA viruses, including influenza, measles and hepatitis C."

In response to a viral infection, RIG-I recognises viral genetic material – specifically, viral RNA – and primes the cell to produce the key anti-viral molecule, interferon. Interferon is secreted and picked up by surrounding cells, causing them to turn on hundreds of genes that act to combat the infection. To understand how RIG-I senses only viral RNA, and not the cell’s own RNA, and sounds the alarm, the scientists used intense X-ray beams generated at the European Synchrotron Radiation Facility (ESRF) to determine the three-dimensional atomic structure of RIG-I in the presence and absence of viral RNA, in a technique called X-ray crystallography. They found that in the absence of a viral infection, the receptor is ‘sleeping with one eye open’: the part of RIG-I that senses viral RNA is exposed, whilst the domains responsible for signalling are hidden, out of reach of the signalling machinery. When RIG-I detects viral RNA, it changes shape, ‘waking up’ the signalling domains, which become accessible to trigger interferon production. Although the EMBL scientists used RIG-I from the mallard duck, this receptor’s behaviour is identical to that of its human counterpart.

"RIG-I is activated in response to viral RNA, but a similar mechanism is likely to be used by a number of other immune receptors, whether they are specific to viruses or bacteria,” says PhD student Eva Kowalinski, who carried out most of the work.

Thus, these findings contribute to a broader understanding of the workings of the innate immune system – our first line of defence against intruders, and the subject of this year’s Nobel Prize in Physiology or Medicine. The work was carried out within the framework of the International Unit of Virus Host-Cell Interactions, a collaboration between EMBL, the University Joseph Fourier (UJF), in Grenoble, and the French Centre National de la Recherche Scientifique (CNRS) and also involved contributions from the laboratory of Denis Gerlier at the Institut National de la Santé et de la Recherche Médicale (INSERM), in Lyon, France.

**Source Article**

**Preventing Dangerous Nonsense in Human Gene Expression**
ScienceDaily (Oct. 13, 2011) — Human genes are preferentially encoded by codons that are less likely to be mistranscribed (or "misread") into a STOP codon. This finding by Brian Cusack and colleagues from the Max Planck Institute for Molecular Genetics in Berlin and the CNRS in Lyon and Paris is published in the open-access journal PLoS Genetics.

Since the completion of the human genome sequence over a decade ago, a multitude of studies have investigated the forces that have shaped the genome over time. However, because gene expression errors are not inherited, they have been disregarded as an evolutionary force until now.

In biological systems, mistakes are made because the cellular machinery is complex and error prone. The errors made in copying DNA for transmission to offspring (genetic mutations) have so far been the primary focus of molecular evolution. But errors are much more frequent in the day-to-day task of gene expression, for example in the transcription of DNA into RNA. This study shows how human genes use a dual strategy of "prevention and cure" to deal with a specific type of gene expression error: transcriptional
errors that create premature STOP codons (so-called "nonsense errors"). Nonsense errors can be highly toxic for the cell, so natural selection has evolved a strategy called nonsense-mediated decay (NMD) to "cure" such errors. However, this cure is inefficient. This work identifies a strategy of prevention that has evolved to compensate for the inefficiency of NMD by decreasing the frequency of nonsense errors. Natural selection achieves this through the avoidance of codons that are prone to nonsense errors and the preferential usage of codons robust to such errors.

Cusack et al's results provide a rationale for the evolution of robustness by implying that transcriptional errors are visible to natural selection because they are frequent and deleterious. According to the authors, "this raises the question of the past and present impact of such errors on human disease." An accompanying Perspectives article is published in PLoS Genetics on the same day.

**Journal Reference:**

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**Schizophrenia Genetics Linked to Disruption in How Brain Processes Sound**

![Image of brain sections](image)

*Staining performed by Konrad Talbot, PhD, targeting a marker for nerve cells involved in inhibition are shown in cross sections of the hippocampus, which is a part of the brain known to be affected in schizophrenia and involved in memory and cognition. In normal mice (top; A and B) a number of inhibitory cells are found. This staining is reduced in mice with reduced dysbindin (bottom; C and D). The finding is identical to that found in tissue from schizophrenia patients and supports the functional finding of the paper that fast inhibitory processes are disrupted in schizophrenia, leading to symptoms of the disease. (Credit: Konrad Talbot, PhD, Perelman School of Medicine, University of Pennsylvania, Neuron)*

ScienceDaily (Oct. 14, 2011) — Recent studies have identified many genes that may put people with schizophrenia at risk for the disease. But, what links genetic differences to changes in altered brain activity in schizophrenia is not clear. Now, three labs at the Perelman School of Medicine at the University of Pennsylvania have come together using electrophysiological, anatomical, and immunohistochemical approaches—along with a unique high-speed imaging technique—to understand how schizophrenia works at the cellular level, especially in identifying how changes in the interaction between different types of nerve cells leads to symptoms of the disease.

The findings are reported this week in the Proceedings of the National Academy of Sciences.

"Our work provides a model linking genetic risk factors for schizophrenia to a functional disruption in how the brain responds to sound, by identifying reduced activity in special nerve cells that are designed to make other cells in the brain work together at a very fast pace" explains lead author Gregory Carlson, PhD, assistant professor of Neuroscience in Psychiatry. "We know that in schizophrenia this ability is reduced, and now, knowing more about why this happens may help explain how loss of a protein called dysbindin leads to some symptoms of schizophrenia."
Previous genetic studies had found that some forms of the gene for dysbindin were found in people with schizophrenia. Most importantly, a prior finding at Penn showed that the dysbindin protein is reduced in a majority of schizophrenia patients, suggesting it is involved in a common cause of the disease.

For the current *PNAS* study, Carlson, Steven J. Siegel, MD, PhD, associate professor of Psychiatry, director of the Translational Neuroscience Program; and Steven E. Arnold, MD, director of the Penn Memory Center, used a mouse with a mutated dysbindin gene to understand how reduced dysbindin protein may cause symptoms of schizophrenia.

The team demonstrated a number of sound-processing deficits in the brains of mice with the mutated gene. They discovered how a specific set of nerve cells that control fast brain activity lose their effectiveness when dysbindin protein levels are reduced. These specific nerve cells inhibit activity, but do so in an extremely fast pace, essentially turning large numbers of cells on and off very quickly in a way that is necessary to normally process the large amount of information travelling into and around the brain.

Other previous work at Penn in the lab of Michael Kahana, PhD has shown that in humans the fast brain activity that is disrupted in mice with the dysbindin mutation is also important for short-term memory. This type of brain activity is reduced in people with schizophrenia and resistant to current therapy. Taken as a whole, this work may suggest new avenues of treatment for currently untreatable symptoms of schizophrenia, says Carlson.

**Journal Reference:**

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**Movement To End Female Genital Cutting Spreads Through Senegal**

The *New York Times* reports on a growing movement in Senegal to end female genital cutting, which was officially banned in the nation more than a decade ago. "The change is happening without the billions of dollars that have poured into other global health priorities throughout the developing world in recent years," the newspaper writes, adding, "Over the past 15 years, the drive to end the practice has gained such momentum that a majority of Senegalese villages where genital cutting was commonplace have committed to stop it."

"[H]ere in Senegal, Tostan, a group whose name means 'breakthrough' in Wolof, Senegal's dominant language, has had a major impact with an education program that seeks to build consensus, African-style, on the dangers of the practice, while being careful not to denounce it as barbaric as Western activists have been prone to do," according to the New York Times. The newspaper highlights some of Tostan's efforts and tells the stories of several Senegalese men and women working with the organization to end the practice in their country. An estimated 92 million girls and women across Africa have undergone genital cutting, according to the newspaper (Dugger, 10/15).

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**Immune peacekeepers discovered**

**How our skin says, 'Don't worry, these are good guys,' revealed today in PNAS**

Sydney: Tuesday 18 October 2011—There are more bacteria living on our skin and in our gut than cells in our body. We need them. But until now no-one knew how the immune system could tell that these bacteria are harmless.

Centenary Institute researchers in Sydney have discovered a set of peacekeepers—immune cells in the outer layers of our skin that stop us from attacking friendly bacteria.

The work will open the way to new therapeutic options for immune-mediated diseases such as inflammatory bowel disease, of which Australia has some of the world’s highest rates.

In a paper published today in the *Proceedings of the National Academy of Sciences* (PNAS), Professor Barbara Fazekas de St Groth and her team have shown that the immune cells in the outer layer of the skin constantly act as peacekeepers to stop the immune system from reacting the way it normally would. Known as Langerhans cells, they resisted every attempt by the researchers to get them to generate an immune response.

The researchers worked with a group of mice in which only the Langerhans cells could stimulate the immune system. They then activated the Langerhans cells and measured the response.

"No matter what we threw at them to get them to activate a long-term immune response, the Langerhans cells always induced immune tolerance," Prof Fazekas says.
This result seems to go against the prevailing wisdom in immunology about the workings of dendritic cells, the class of immune cell to which Langerhans cells belong.

Dendritic cells engulf bacteria, viruses or other invaders and put a marker from that invader, known as an antigen, on a protein that can bind to other immune cells.

The antigen reprograms passing T cells, the workhorses of the immune system, which then set off a cascade of responses that eventually lead to the destruction of anything displaying that antigen.

However, the Centenary team (which is affiliated with the University of Sydney and RPA Hospital) found Langerhans cells are very different from other dendritic cells: after turning on the helper T cells, they tell them to self-destruct instead.

"This is the opposite of what you'd usually expect. In previous studies of immune cells, if there was a flurry of activity, we assumed it was the start of a long-term immune response," Prof Fazekas says.

However, the immune system is a layered defence—-the next layer of skin has different kinds of dendritic cells, which program on-going responses against bacteria. So if bacteria penetrate deep enough to meet these cells, the immune response will kill them.

In inflammatory bowel disease, which afflicts thousands of Australians, the immune system is activated against the gut bacteria, which are usually left alone.

This discovery opens up possible ways to figure out why this disorder occurs and to find treatments to a range of diseases of the immune system.

"There is so much we don't know about the immune system, but sometimes just mimicking what the system does, like we do with vaccines, can work very well" Prof Fazekas says,

"If we do manage to mimic what Langerhans cells do, then we could develop treatments that would precisely tolerise against specific antigens — just like the immune system of the skin does now."

Centenary Institute executive director Professor Mathew Vadas says this latest paper comes just weeks after Centenary researcher Patrick Bertolino made the front cover of PNAS for his paper on immune response in the liver.

"The Centenary Institute is interested in understanding how the immune system works—these discoveries and others already in the pipeline here are a major step forward towards that goal," Prof Vadas says.

**Cells are crawling all over our bodies, but how?**

**Biologists at Florida State devise new way to watch how cells move**

For better and for worse, human health depends on a cell's motility — the ability to crawl from place to place. In every human body, millions of cells — are crawling around doing mostly good deeds — though if any of those crawlers are cancerous, watch out.

"This is not some horrible sci-fi movie come true but, instead, normal cells carrying out their daily duties," said Florida State University cell biologist Tom Roberts. For 35 years he has studied the mechanical and molecular means by which amorphous single cells purposefully propel themselves throughout the body in amoeboid-like fashion — absent muscles, bones or brains.

they use the millions of tiny filaments found on their front ends to push the front of their cytoskeletons forward. In rapid succession the cells then retract their rears in a smooth, coordinated extension-contraction manner that puts inchworms to shame. Yet take them out of the body and put them under a microscope and the crawling changes or stops.

But now Roberts and his research team have found a novel way around uncooperative human cells.

In a landmark study led by Roberts and conducted in large part by his then-FSU postdoctoral associate Katsuya Shimabukuro, researchers used worm sperm to replicate cell motility in vitro — in this case, on a microscope slide.

Doing what no other scientists had ever successfully done before, Shimabukuro disassembled and reconstituted a worm sperm cell,
then devised conditions to promote the cell's natural pull-push crawling motions even in the unnatural conditions of a laboratory. Once launched, the reconstituted machinery moved just like regular worm sperm do in a natural setting — giving scientists an unprecedented opportunity to watch it move.

Roberts called his former postdoc's signal achievement "careful, clever work" — and work it did, making possible new, revealing images of cell motility that should help to pinpoint with never-before-seen precision just how cells crawl.

"Understanding how cells crawl is a big deal," Roberts said. "The first line of defense against invading microorganisms, the remodeling of bones, healing wounds in the skin and reconnecting of neuronal circuits during regeneration of the nervous system — all depend on the capacity of specialized cells to crawl.

"On the downside, the ability of tumor cells to crawl around is a contributing factor in the metastasis of malignancies," he said. "But we believe our achievements in this latest round of basic research could eventually aid in the development of therapies that target cell motility in order to interfere with or block the metastasis of cancer."

Funding for Robert's worm-sperm study came from the National Institutes of Health. The findings are described in a paper ("Reconstitution of Amoeboid Motility In Vitro Identifies a Motor-Independent Mechanism for Cell Body Retraction") published online in the journal *Current Biology*.

Why worm sperm?

For one thing, said Roberts, the worm sperm is different from most cells in that it doesn't use molecular motor proteins to facilitate its contractions; it shimmies along strictly by putting together and tearing down its tiny filaments. And the simple worm sperm makes a good model because, while it is similar to a human cell it has fewer moving parts, making it less complicated to take apart and reassemble than, say, brain or cancer cells.

Armed with the newfound ability to reconstitute amoeboid motility in vitro, cell biologists such as Roberts may be able to learn the answers to some major moving questions. Among them: How can some cells continue to crawl even after researchers have disabled their supply of myosin, the force-producing "mover protein" that functions like a motor to help power muscle and cell contraction?

For Roberts and his team, the next move will be to determine if what they've learned about worm sperm also applies to more conventional crawling cells, including tumor cells.

"As always, there will be more questions," Roberts said. "Are there multiple mechanisms collaborating to drive cell body retraction? Is there redundancy built into the motility systems?"

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**First results from Phase 3 trial show malaria vaccine candidate reduces the risk of malaria** *(long)*

**First results from ongoing Phase III trial show malaria vaccine candidate, RTS,S* reduces the risk of malaria by half in African children aged 5 to 17 months**

Seattle, 18 October 2011 — First results from a large-scale Phase III trial of RTS,S, published online today in the *New England Journal of Medicine* (NEJM), show the malaria vaccine candidate to provide young African children with significant protection against clinical and severe malaria with an acceptable safety and tolerability profile. The results were announced today at the Malaria Forum hosted by the Bill & Melinda Gates Foundation in Seattle, Washington.

**5 to 17 month-old children**

The trial, conducted at 11 trial sites in seven countries across sub-Saharan Africa, showed that three doses of RTS,S reduced the risk of children experiencing clinical malaria and severe malaria by 56% and 47%, respectively. This analysis was performed on data from the first 6,000 children aged 5 to 17 months, over a 12-month period following vaccination. Clinical malaria results in high fevers and chills. It can rapidly develop into severe malaria, typified by serious effects on the blood, brain, or kidneys that can prove fatal. These first Phase III results are in line with those from previous Phase II studies.

The widespread coverage of insecticide-treated bed nets (75%) in this study indicated that RTS,S can provide protection in addition to that already offered by existing malaria control interventions.

**6 to 12 week-old infants**

The trial is ongoing and efficacy and safety results in 6 to 12 week-old infants are expected by the end of 2012. These data will provide an understanding of the efficacy profile of the RTS,S malaria vaccine candidate in this age group, for both clinical and severe malaria.

**Combined data in 6 to 12 week-old infants and 5 to 17 month-old children**
An analysis of severe malaria episodes so far reported in all 15,460 infants and children enrolled in the trial at 6 weeks to 17 months of age has been performed. This analysis showed 35% efficacy over a follow-up period ranging between 0 and 22 months (average 11.5 months).

**Long-term efficacy**
The RTS,S malaria vaccine candidate is still under development. Further information about the longer-term protective effects of the vaccine, 30 months after the third dose, should be available by the end of 2014. This will provide evidence for national public health and regulatory authorities, as well as international public health organisations, to evaluate the benefits and risks of RTS,S.

**Safety**
The overall incidence of serious adverse events (SAEs)** in this trial was comparable between the RTS,S candidate vaccine (18%) recipients and those receiving a control vaccine (22%). Differences in rates of SAEs were observed between the vaccines groups for specific events, such as seizures and meningitis, and were higher in the malaria vaccine group. Seizures were considered to be related to fever and meningitis was considered unlikely to be vaccine-related. These events will continue to be monitored and additional information about the safety profile of the RTS,S malaria vaccine candidate will become available over the next three years.

**Tsiri Agbenyega, a principal investigator of the trial and Chair of the Clinical Trials Partnership Committee, said:** "The publication of the first results in children aged 5 to 17 months marks an important milestone in the development of RTS,S. These results confirm findings from previous Phase II studies and support ongoing efforts to advance the development of this malaria vaccine candidate. Having worked in malaria research for more than 25 years, I can attest to how difficult making progress against this disease has been. Sadly, many have resigned themselves to malaria being a fact of life in Africa. This need not be the case. Renewed interest in malaria by the international community, and scientific evidence such as that we are reporting today, should bring new hope that malaria can be controlled."

**Andrew Witty, CEO, GSK, said:** "These data bring us to the cusp of having the world's first malaria vaccine, which has the potential to significantly improve the outlook for children living in malaria endemic regions across Africa. The addition of a malaria vaccine to existing control interventions such as bed nets and insecticide spraying could potentially help prevent millions of cases of this debilitating disease. It could also reduce the burden on hospital services, freeing up much needed beds to treat other patients who often live in remote villages, with little or no access to healthcare. Today's results are a testament to the dedication and tenacity of many scientists, led at GSK by Jean Stéphenne and his vaccine team, including Joe Cohen, the co-inventor of RTS,S, in partnership with many others from across the world. Development is however only half the task, but GSK remains committed to further research into malaria and most importantly, to ensuring that this vaccine will reach those who need it."

**Christopher Elias, president and CEO of PATH , said:** "This trial represents a powerful example of the high-quality science that is moving us toward controlling and someday potentially eliminating malaria. The results made public today are encouraging and certainly something to feel good about, but let's also remember the human dimension. The PATH Malaria Vaccine Initiative's mission is to deliver a vaccine to the children of Africa so that instead of carrying near lifeless babies to crowded pediatric wards, mothers will carry their infants past noisy school playgrounds to bustling immunization clinics. Today, we are an important step closer to realizing that vision, and we look forward to continuing our drive, together with our partners, to bring this vaccine home to the children of Africa."

**Bill Gates, co-chair of the Bill & Melinda Gates Foundation, said:** "A vaccine is the simplest, most cost-effective way to save lives. These results demonstrate the power of working with partners to create a malaria vaccine that has the potential to protect millions of children from this devastating disease."

The vaccine is being developed in partnership by GSK and the PATH Malaria Vaccine Initiative (MVI), together with prominent African research centers. The partners are all represented on the Clinical Trials Partnership Committee, which is responsible for the conduct of the trial. Major funding for clinical development comes from a grant by the Bill & Melinda Gates Foundation to MVI. An extended team of organisations continues to work on RTS,S, including scientists from across Europe, North America and Africa. Should it be approved by regulatory authorities and recommended by the World Health Organisation (WHO), it will be used for African children, who are most at risk from the disease. Successful development of an effective vaccine to be used alongside other measures such as bed nets and anti-malarial medicines would represent a decisive step toward sustained malaria control.
The impact of the RTS,S Phase III trial extends beyond the vaccine being researched. The trial has made a considerable contribution to many of the African communities that host the trial sites through improved healthcare and hospital facilities. Research capacity at many of the research centres has been strengthened through the training of staff, provision of state-of-the-art laboratories, equipment, and construction of new facilities. This enhanced capacity bodes well for the centres to expand further their leadership in developing remedies for malaria and other infectious diseases for years to come.

**Looking ahead**

GSK and MVI are committed to making this vaccine available to those who need it most, should it be approved and recommended for use. In January 2010, GSK announced that the eventual price of RTS,S will cover the cost of manufacturing the vaccine together with a small return that will be reinvested in research and development for second-generation malaria vaccines or vaccines against other neglected tropical diseases.

If the required public health information, including safety and efficacy data from the Phase III programme, is deemed satisfactory, the WHO has indicated that a policy recommendation for the RTS,S malaria vaccine candidate is possible as early as 2015, paving the way for decisions by African nations regarding large scale implementation of the vaccine through their national immunisation programmes.

**40% of cancers may be caused by viruses**

Up to forty percent of cancers, including brain tumors and leukemia, may be caused by viruses, scientists claim.

If they are proved correct in further tests, it could pave the way for vaccinations against several types of cancer and therapies to cure them.

The claim follows research which has discovered viruses in types of cancer which were never thought to have been linked with infection.

It has been known for decades that viruses cause some types of cancer but it was thought to be only 10 to 20 per cent of cases.

The best known are the hepatitis B and C bugs, which can cause liver cancer, and the human papilloma virus (HPV) which can cause cervical cancer.

Last week scientists at the Karolinska Institute in Sweden found a viral link with medulloblastoma, the most common form of childhood brain tumor.

It follows the discovery two years ago that Merkel cell carcinoma, an aggressive skin cancer, often follows infection by the polyomavirus which is common among animals and can spread to humans.

It is also claimed that prostate cancers could be caused by viruses.

Nobel Prize winner Harald zur Hausen, who jointly discovered the link between cervical cancer and HPV in the 1980s, said he expected more discoveries to follow and suggested that viruses could be involved in cancer of the skin, breast, gut and lungs.

But scientists warn it could take a long time and huge investment before vaccines are developed.

Alan Rickinson, professor of cancer studies at Birmingham University, said: ‘If we can understand how these viruses work we could prevent people from contracting them and even create therapies that use the patient’s own immune system to destroy infected or cancerous cells.’

The process still confounds experts because viruses work by invading cells and making them produce more viruses. But this process then kills the cell which should mean it cannot become cancerous.

One theory is that cancer-causing viruses can remain hidden in cells for years, preventing the cell from repairing mutations.

**Possible Causes Of Various Cancers**

- **Hepatitis B and C** – both cause liver cancer
- **Human Papilloma virus** – Causes cervical cancer
- **Merkel cell polyomavirus** – skin cancer
- **Cytomegalovirus** – could cause childhood brain tumours
- **Epstein-Barr virus** – causes blood and lymph system cancers
- **XMRV** – possible link to prostate cancer

Via [Daily Mail](http://www.dailymail.co.uk)
Fish pedicures unlikely to cause HIV infection
Roger Pebody
Published: 18 October 2011

The Daily Mail and the Sun are alarming their readers today with articles alleging that “fish foot spa pedicures could spread HIV and hepatitis C” and that there is a “fish foot spa virus bombshell”. The story has been picked up other media outlets, including Fox News, the Times of India and the Daily Telegraph. However the stories mostly twist and distort the source they are based on, a set of recommendations from the Health Protection Agency (HPA) on the management of fish pedicures and fish spas. Indeed, the HPA titled their press release: “Fish pedicures unlikely to cause infection.”

There are no known cases of HIV infection due to the use of fish spas, or indeed from any other water-borne route.

An increasing number of salons and beauty therapists offer ‘fish pedicures’ in the UK. They involve immersing the feet in a tank of water containing Garra rufa fish (a small toothless species of freshwater carp) that nibble off dead and thickened skin. The use of Garra rufa fish is long established in Turkey, India and the Far East where it has a history as a treatment for a variety of skin conditions and, more recently, as a cosmetic treatment for the removal of dead and hardened skin from the feet.

While there is little evidence in scientific literature of the potential public health risk to users, some are concerned about the presence of bacteria in the fish tank water. Moreover, while the fish are only meant to nibble dead skin, some clients may occasionally bleed into the water, raising anxieties about the transmission of blood borne viruses.

There are restrictions on the practice in Germany and 18 states of the USA. Four Canadian provinces have banned the procedure on the grounds that fish used as ‘instruments’ for pedicures cannot be disinfected or sterilised between clients.

The HPA’s report examines the available evidence and scientific plausibility for the transmission of blood borne viruses from person to person, via the water in the fish tank. Hepatitis B and C survive outside the body for longer than HIV and the only suspected blood borne virus transmission cases via water relate to hepatitis B.

An infected client would need to bleed from an open cut, abrasion or wound into the water, and then another client would need to also have an open cut, abrasion or wound for the infected blood to enter his or her bloodstream. Importantly, the concentration of virus would be substantially reduced by the diluting effect of the water.

If virus contaminated a fish’s mouth, it would be unlikely to remain on the mouth and effect a transmission to the next client. Moreover a fish cannot itself be infected with the human immunodeficiency virus (and there is no “fish equivalent” of HIV).

Overall, the HPA describe the risk of blood borne virus infection as “extremely low”, although it cannot be completely excluded.

They do make a number of hygiene recommendations for operators of fish spas (e.g. refreshing the water supply). To reduce the risk of infections being passed on or picked up, clients who have broken skin, athlete’s foot, a verruca, psoriasis or eczema affecting the feet or lower legs should not have fish pedicures.

Similarly, they advise that people with HIV (and hepatitis B or C) should not have fish pedicures. However it is not clear what scientific evidence this recommendation is based on or whether it is a proportional response to this theoretical transmission risk.

Lisa Power of the Terrence Higgins Trust dismissed the media’s concern about the issue: “The reality is, in this country, too many people are contracting HIV because they aren’t using condoms, not because they’re going for fish pedicures.”

Many French Physicians Find Rapid HIV Testing Infeasible
Daniel M. Keller, PhD

October 18, 2011 (Belgrade, Serbia) — In the first study to evaluate the feasibility of rapid HIV testing by primary care physicians in private practice in France, physicians had trouble drawing blood and preparing the sample, and complained of time constraints. At this point, these factors appear to be significant barriers to rapid testing in physicians offices, Raphael Gauthier, MD, from the Department of General Medicine at the University of Paris, France, told delegates here at the 13th European AIDS Conference of the European AIDS Clinical Society.

He explained that rapid HIV testing is new in France, that training is needed to ensure quality control, and that an improved test with a simplified sampling method could possibly overcome the barriers.
Generally, three quarters of the 5 million HIV screening tests are performed by private laboratories with a physician's prescription. About 6700 new infections are diagnosed each year (a yield of about 0.13%).

"Despite this screening activity, the proportion of people unaware they that are infected with HIV remains high, and a third of the newly diagnosed patients access care [with a] late presentation of their HIV disease," Dr. Gauthier said. He estimates that there are 50,000 people in France who are unaware that they are seropositive.

French HIV testing guidelines updated in 2008 recommended routine testing, and on the basis of many studies from the United States, rapid HIV testing has been encouraged for every primary care venue in France. However, it was not clear whether such a plan would be feasible in private practices in Europe.

Thus, Dr. Gauthier and colleagues designed a study to determine the feasibility and acceptability of screening with a rapid HIV test in French private physicians offices and to identify any difficulties with the procedure.

This prospective study was performed in physicians' offices over 30 working days from June to October 2010. The physicians were affiliated with HIV healthcare networks, but were not working in sexually transmitted infection or genitourinary medicine clinics. All were trained in the use of the rapid test, and all adults tested were covered by medical insurance.

Patients waiting to see a physician were informed that they could have a rapid HIV test. Those accepting the offer or consenting after a physician recommendation were tested with the Vikia HIV 1/2 test, using finger-stick whole blood. The blood was collected in a capillary tube and tested in a disposable chromatographic device; the result was available in 30 minutes.

Physicians (84 general practice, 6 dermatology, 1 gynecology) recruited 383 patients (48.8% female) with a mean age of 36.2 years (range, 18 to 86 years), and 382 patients completed the test, for an acceptance rate of 99.7%. About two thirds of the tests were done at the patient's request; the rest were done at the physician's recommendation.

Of 378 test results, 92.1% were negative and 7.9% were invalid; 41.9% of doctors had difficulty with the test. Of those having difficulties, "the main problem was the blood sampling technique," Dr. Gauthier said. Physicians reported various difficulties: "the inefficacy of the microlancet to draw enough blood, blood not coming easily into the capillary tube, and air formation or blood coagulation in the capillary." Almost 92% of the problems that physicians reported involved blood sampling.

Thirty test results were invalid, 90% of which were associated with physicians' difficulties in performing the tests.

"We believe that those invalid tests correspond to the extreme cases of blood sampling difficulty, where the physicians could not obtain the 75 μL of blood necessary to perform the test," Dr. Gauthier explained. "Those results came from 19 physicians. The demographic data and participation data are similar to the rest of the investigator population, but we observed that two thirds of them attended the training session in Paris. So we can assume that this training session failed in some way to provide them a complete technical competency."

Seventy-two physicians filled out a poststudy questionnaire, and about 40% said they would not continue to use the rapid test in their daily practices, citing blood sampling issues (43.1%), time constraints (12.5%), and various other barriers.

Session chair Georg Behrens, MD, professor of immunology at Hanover Medical School in Germany, told Medscape Medical News that "this study shows that physicians are a main barrier to HIV testing."

He said that more rapid tests might not overcome this barrier because testing is an extra effort in a general practice. "The immediate feedback is that you need a lot of tests to get 1 positive one. I think that many [general practitioners] will give up over time, rather than using even a shorter test system," he said. In essence, the yield and reward are just not there to justify doing the tests.

Dr. Behrens pointed out that patients are interested in rapid testing because of the quick result. He suggested that a better alternative is to contact the patient by telephone: "I think it's a good way to have a connection...to get [the patient] back into the clinic and then discuss the results." Such a system would require accurate contact information for the patient and assigning someone to do the follow-up. Dr. Behrens said he thinks a better alternative to universal rapid testing in physicians' offices, with potentially higher yields, is to "go into high-risk groups and other settings."

Haiti Has Highest Rate Of Cholera Worldwide One Year After Disease Outbreak Began

Paul Farmer, a founder of Partners in Health (PIH) and U.N. deputy special envoy to Haiti, in an interview with the Associated Press/Washington Post "said cholera has sickened more than 450,000 people in a nation of 10 million, or nearly five percent of the population, and killed more than 6,000," giving the Caribbean nation "the highest rate of cholera in the world a mere year after the disease first arrived" (10/18).

The Pan American Health Organization (PAHO) "expects the epidemic to ease partially, but nonetheless predicts a further 250,000 cases next year, says Peter Graaff, the PAHO/World Health Organization (WHO) representative in Haiti," Nature News writes. The news service notes that two groups, Medecins Sans Frontieres (MSF) and GHEKIO in conjunction with PIH, plan on including a cholera vaccine in their emergency responses over the coming months (Butler, 10/18). "Despite the spread of cholera, Farmer said it was possible to wipe out the disease by improving Haiti’s water system and sanitation. The use of education and oral vaccines is also important, he added," the AP writes (10/18).

HIV Advocates In Uganda 'Losing Faith' As Country Works To Prevent, Treat New Infections, PlusNews Reports

PlusNews examines how "corruption scandals, frequent treatment shortages and accusations of a misguided prevention program" have undermined progress in the fight against HIV/AIDS in Uganda, a country that had "won plaudits in the early days of the epidemic for the aggressive stance taken by President Yoweri Museveni." Uganda "lowered its HIV prevalence from 18 percent in the early 1990s to about six percent in 2000," the news service notes. According to PlusNews, "Some of Uganda's most active campaigners in its 30-year fight against HIV are losing faith in the government's ability to effectively counter the epidemic as the country struggles to provide treatment and prevent more than 100,000 new infections every year."

The news service speaks with a number of HIV/AIDS advocates in the country who cite the president’s support of prevention programs that do not emphasize condom use, the questioning of evidence-backed prevention techniques such as medical male circumcision, a lack of proper coordination at the top of the HIV response, and the exclusion of grassroots communities in high-level HIV decision-making as issues that have led to "disorganization" and "stagnation" in the country's HIV response (10/18).

New therapy protects monkeys from Hendra virus

GALVESTON, Texas — A new treatment for the deadly Hendra virus has proven successful in primate tests — a major step forward in combating the virus, which kills about 60 percent of those it infects and has been implicated in sporadic outbreaks in Australia ever since it was first identified in 1994.

Researchers from the University of Texas Medical Branch at Galveston, Rocky Mountain Laboratories, the National Institute of Allergy and Infectious Diseases, the National Institutes of Health, the Uniformed Services University of the Health Sciences, the National Cancer Institute, and the Boston University School of Medicine teamed up to develop and test the new therapy, in a project primarily supported by a grant awarded to UTMB professor Thomas Geisbert by the NIAID.

Experiments were conducted at RML in a biosafety level 4 "spacesuit" lab, because no licensed vaccine or therapy currently exists for Hendra. Researchers infected 14 African green monkeys — chosen because their response to Hendra is very similar to that of humans — with the virus. At varying time intervals after infection, 12 of the monkeys were then given doses of a human antibody designated m102.4, which had been specially selected for its affinity for Hendra.

Earlier test tube and small-animal experiments by USUHS professor Christopher Broder and colleagues in Australia had strongly suggested that m102.4 antibodies would bind to proteins on the surface of Hendra virus particles and block the process by which the virus invades cells. This turned out to be the case with the monkeys as well, and all 12 of the treated animals survived — including a group not given their first dose of antibodies until three days after infection with Hendra.

"I think this is a very promising therapy, especially when you consider that it was still strong three days later," said Geisbert, one of the lead authors of a paper on the work published online Oct. 19 in Science Translational Medicine. "What's also interesting is that this antibody has strong activity against Nipah virus as well, which is extremely similar to Hendra."
Both Hendra and Nipah primarily reside in fruit bats, and both are extraordinarily dangerous to humans. (If the virus names sound familiar to moviegoers, it's not an accident: director Stephen Soderbergh used an imaginary combination between Hendra and Nipah to create the virus in the recent film Contagion.) But while Hendra primarily affects horses, which can spread the disease to humans, Nipah has evolved to be transmissible directly from human to human. First identified in Malaysia in 1998, Nipah is blamed for 251 deaths in outbreaks in Malaysia, India and Bangladesh.

"Here at UTMB’s Galveston National Laboratory we’re currently looking at the efficacy of this antibody against Nipah," Geisbert said. "That would make it even more valuable."

Last year m102.4 was requested for emergency use in Australia to protect a woman and her daughter from an exposure to Hendra. Both survived and showed no side effects from the treatment.

Much more extensive testing would be required, though, to obtain approval for m102.4 as a therapy. According to GNL director James LeDuc, the facility is well prepared to move forward with such efforts.

"Collaboration between federal and university scientists has been instrumental in producing this novel breakthrough," LeDuc said. "We’re ready to help in the next steps in translating this discovery into a usable treatment."

Diseases of ageing occurring 10 to 15 years earlier in patients with HIV
Michael Carter
Published: 20 October 2011

The diseases of ageing develop earlier in patients with HIV than in the general population, Italian investigators report in the online edition of Clinical Infectious Diseases.

“Our findings suggest that an aggressive approach to the screening, diagnosis, and treatment of non-infectious comorbidities is warranted as part of the routine healthcare for HIV-infected patients,” comment the investigators. “Our data suggest that onset of such screening should commence at a substantially earlier age for HIV-infected persons, compared with HIV-uninfected persons, possibly at least a decade in advance.”

Effective antiretroviral therapy can significantly improve the life expectancy of patients with HIV. However, even with treatment mortality rates are still higher than those observed in the general population.

Non-infectious conditions such as cardiovascular disease, hypertension, diabetes, renal failure and liver disease are increasingly important causes of illness and death in patients with HIV. These illnesses are often associated with ageing.

This has led some investigators to suggest that patients with HIV experience premature ageing. Doctors from the Metabolic Clinic of Modena University, Italy, wanted to examine this theory. They therefore designed a study comparing the prevalence and risk factors for several common age-related conditions in their HIV-positive patients, compared to age, race and sex-matched controls.

Preliminary findings from this study were presented at the 18th Conference on Retroviruses and Opportunistic Infections in March 2011.

A total of 2854 patients who received care at the clinic between 2002 and 2009 were included in the analysis. All had experience of HIV therapy. Their mean age was 46 years, 37% were women and three-quarters had lipodystrophy – the body fat changes associated with some antiretroviral drugs. The patients were matched with 8562 controls.

The non-infectious comorbid conditions included in the analysis were cardiovascular disease, hypertension, diabetes, bone fracture, and renal failure. Data were also gathered on the prevalence of multiple conditions.

Rates of cardiovascular disease were higher among HIV-positive patients than the controls for individuals aged below 40 (0.91% vs. 0.24%, p = 0.049), as well as those between the ages of 41 and 50 (2.26% vs. 0.64%, p < 0.01), and the ages of 51 to 60 (6% vs. 2.6%; p = 0.02).

There was also a higher prevalence of hypertension in the HIV-positive patients aged over 51 compared to the controls (ages 51 to 60, 20% vs. 17%; p = 0.18; age 60+, 39% vs. 32%, p = 0.007).

In all age groups, there was a significantly higher prevalence in the HIV-positive patients of renal failure, bone fracture, and diabetes (all p < 0.001).

Moreover, across all age strata the HIV-infected patients were more likely to have multiple diseases of ageing. Strikingly, the prevalence of two or more comorbid conditions in HIV-positive patients aged
between 41 and 50 was 9%, similar to the 7% prevalence observed in HIV-negative controls in the 51 to 60 age bracket.

“The prevalence...was approximately equivalent to prevalence observed in members of the public who were 10 to 15 years older,” write the authors. “We believe that, in this report, by showing the premature onset of polyopathy among HIV-infected patients, we have contributed to the characterization of an emerging description of an HIV-specific aging phenotype.”

Across the entire cohort, the factors associated the presence of multiple diseases of aging were age (per 1 year increase, OR = 1.11; 95% CI, 1.10-1.12, p < 0.001), male sex (OR = 1.77; 95% CI, 1.44-2.17, p < 0.001), a lowest ever CD4 cell count below 200 cells/mm³ (OR = 4.46; 95% CI, 3.73-5.34, p < 0.001), and length of exposure to HIV therapy (OR = 1.01; 95% CI, 1.001-1.019, p = 0.001).

Further analysis also showed an association with lipodystrophy (p = 0.048).

“At any given age, HIV-infected patients had a greater likelihood of comorbidities than did control subjects,” Dr Jacqueline Capeau, the author of an editorial accompanying the study notes. "Why? Is the entire aging process accelerated in these patients? Are all HIV-infected patients aging too rapidly? What can be done?"

She suggests that the chronic inflammation and immune activation accompanying HIV infection means “patients will be more prone to develop, in advance, age-related diseases.” A low nadir CD4 cell count could further contribute to inflammatory process.

Dr Capeau also notes that the study population comprised patients treated at a metabolic clinic with a high prevalence of lipodystrophy. She suggests that these patients are likely to have been severely immune depressed when they initiated antiretroviral therapy. Moreover, their treatment would have been based on more toxic anti-HIV drugs.

“These...patients have accumulated deleterious conditions and are now affected by comorbidities,” writes Dr Capeau.

Life-style factors such as smoking, a poor diet, and drug use are also proposed as possible causes of possible causes.

“It is important to diagnose and treat these comorbid conditions,” Dr Capeau emphasises, and she proposes the wider use of anti-inflammatory drugs such as aspirin and statins. In addition, “early treatment of HIV-infected patients may help to delay aging.”

Reference

Vaccines Among Most Successful, Cost-Effective Health Investments In History
"Vaccines are among the most successful and cost-effective health investments in history," Seth Berkley, CEO of the GAVI Alliance, writes in this post in the Huffington Post’s "Impact" blog. Because vaccines have saved millions of lives, "donors, the global health community and developing countries themselves [must] stay focused on immunization," he writes.

Though that "is a tough challenge for donor governments who are facing very real and very serious budget deficits ... Republicans and Democrats have an unprecedented opportunity to demonstrate their continued cooperation on cost-effective health solutions for poorer nations that yield real results" by "continu[ing] the decade-long, bipartisan collaboration [for] championing global immunization," Berkley states. "The return on investment in global health is tremendous, and the biggest bang for the buck comes from vaccines," he writes, concluding, "For just a small percentage of the total foreign assistance program, which in itself makes up just one percent of the federal budget, the U.S. can lead a transformation in child health and survival around the world" (10/19).

India Must Stay The Course In Efforts To Eradicate Polio
"Clearly, there is no room for complacency" in India’s efforts to eradicate polio, defined by the WHO as no recorded case of the disease for three years, because "[t]he goal of complete eradication is within reach," Deepak Gupta, a senior U.N. professional in Strategic Health/Development Communication, writes in an Asia Sentinel opinion piece. "[T]he next three years—till 2014—will be crucial," he writes, meaning experts should focus on "intense communication and preventive work, especially with regard to critical risk-factors like poor routine immunization and lack of proper sanitation," he states, concluding, "The challenge is to ensure the sustainability of the success achieved so far" (10/19).
West Nile virus transmission linked to land use patterns and 'super-spreaders'
Robins play a key role in transmission of West Nile virus across much of North America

SANTA CRUZ, CA—After its initial appearance in New York in 1999, West Nile virus spread across the United States in just a few years and is now well established throughout North and South America. Both the mosquitoes that transmit it and the birds that are important hosts for the virus are abundant in areas that have been modified by human activities. As a result, transmission of West Nile virus is highest in urbanized and agricultural habitats.

"The virus has had an important impact on human health in the United States partly because it took advantage of species that do well around people," said Marm Kilpatrick, a biologist at the University of California, Santa Cruz, who studies the ecology of infectious diseases.

West Nile virus can infect a wide range of animals, including more than 300 species of birds and 60 species of mosquitoes. It also infects mammals, reptiles, and even amphibians. But researchers have found that in most places only a few key species of bird "hosts" and mosquito "vectors" are important in transmission of the virus.

"We now know that in any given location, only one or two species of mosquitoes play a big role, and only a handful of birds appear to be important in overall transmission rates," said Kilpatrick, who reviewed a decade of research on the ecology and evolution of West Nile virus in a paper published in the October 21 issue of Science.

According to Kilpatrick, the familiar American robin plays a key role in the transmission of West Nile virus across much of North America. It is such an important host species that Kilpatrick calls robins "super-spreaders" of West Nile virus. The reason is not so much the abundance of robins, but rather the feeding patterns of the mosquitoes that transmit the virus. The mosquito species important in transmission seem to prefer robins over other, more abundant species of birds such as house sparrows.

"Robins are more important in transmission than their abundance alone would suggest," Kilpatrick said. "The peculiar feeding habits of the vectors play a really important role in transmission, and this idea applies to many different diseases. It's one of the really interesting things we've learned from the past decade of research on West Nile virus."

Insights gained from research on West Nile virus could help public health officials deal with other introduced diseases in the future. "The spread of disease-causing organisms is likely to only increase in the coming years," said Sam Scheiner, director of the Evolution and Ecology of Infectious Diseases program at the National Science Foundation (NSF). "West Nile virus has provided a test of our ability to respond to such spread. This research shows that predicting disease incidence in humans and other animals is more complex than first imagined, but that greater understanding of such complexities is possible—knowledge that can be applied to the next threat."

The globalization of trade and travel has spread many invasive species, including infectious pathogens like West Nile virus. Although its exact route of entry to New York is unknown, West Nile virus may have arrived in an infected mosquito carried across the Atlantic by an airplane, Kilpatrick said. The virus then adapted quickly to its new environment, evolving a new strain that was transmitted more efficiently by local mosquitoes than the introduced strain. By 2005, the new strain had completely displaced the introduced one throughout North America.

Three species of mosquitoes are key vectors for transmitting West Nile virus in much of North America. Interestingly, these mosquitoes are not among the species that feed frequently on people. They are bird specialists that happen to bite people often enough to cause human infections. "The mosquitoes that bite humans most are actually not as important in transmission of West Nile virus to humans because they rarely bite birds and thus rarely get infected in the first place," Kilpatrick said. "Instead, it's the species that feed mostly on birds and frequently get infected, but occasionally feed on people, that are most important."

Millions of birds have died from West Nile virus infection, with dramatic effects on the populations of some species. Crows, for example, are much less abundant than they were before the virus arrived. The robin population, which had been growing rapidly, has leveled off.

"Robins were on a steady upward trajectory thought to be linked to human land use—they love lawns and agricultural fields," Kilpatrick said. "Crow populations were growing even faster. Now crow populations have crashed downward and robins have leveled off, and we suspect that's due to West Nile virus."
The worst human outbreaks of West Nile virus in the United States occurred in 2002 and 2003. According to Kilpatrick, it’s not clear whether the reduction in human disease since then represents a long-term trend or short-term variability. "It may be that with climatic conditions favorable for the virus we could again get very intense years of transmission," he said. "We don't know yet how much of the year-to-year variation can be explained by climatic conditions or other factors, such as acquired immunity in birds or humans."

Many other diseases caused by mosquito-borne or tick-borne viruses could potentially be introduced to the United States from overseas, Kilpatrick said. Understanding the ecology of these viruses may lead to strategies that could prevent a newly introduced pathogen from establishing itself as successfully as West Nile virus has.

**First Ebola-like virus native to Europe discovered**

**New virus could be the first filovirus to cause disease in bats**

A team of international researchers has discovered a new Ebola-like virus — Lloviu virus — in bats from northern Spain. Lloviu virus is the first known filovirus native to Europe, they report in a study published in the journal *PLOS Pathogens* on October 20th.

The study was a collaboration among scientists at the Center for Infection and Immunity (CII) at Columbia University’s Mailman School of Public Health, the Instituto de Salud Carlos III (ISCIII) in Spain, Roche Life Sciences, Centro de Investigación Príncipe Felipe, Grupo Asturiano para el Estudio y Conservación de los Murciélagos, Consejo Superior de Investigaciones Científicas and the Complutense University in Spain.

Filoviruses, which include well-known viruses like Ebola and Marburg, are among the deadliest pathogens in humans and non-human primates, and are generally found in East Africa and the Philippines. The findings thus expand the natural geographical distribution of filoviruses.

"The study is an opportunity to advance the knowledge of filoviruses’ natural cycle," said Ana Negredo, one of the first authors of the study.

Scientists at ISCIII analyzed lung, liver, spleen, throat, brain and rectal samples from 34 bats found in caves in Asturias and Cantabria, Spain, following bat die-offs in France, Spain and Portugal in 2002 affecting mainly one bat species.

They screened these samples for a wide range of viruses using the polymerase chain reaction, a molecular technique that allows scientists to amplify genetic material, and detected a filovirus. Filoviruses include ebolaviruses and marburgviruses, two viruses associated with severe disease in humans and other primates.

CII scientists used high-throughput sequencing to characterize the virus’ genome. When they compared it to other well-known filovirus genomes, they found that Lloviu virus represents a class of viruses distantly related to all ebolaviruses and that it may have diverged from ebolaviruses about 68,000 years ago.

"The detection of this novel filovirus in Spain is intriguing because it is completely outside of its previously described range. We need to ascertain whether other filoviruses native to Europe exist, and more importantly, if and how it causes disease," said Gustavo Palacios, the other first author of the study.

Filoviruses typically do not make bats sick, but because the team of researchers only detected Lloviu virus in bats that had died and whose tissues showed signs of an immune response, they think Lloviu may be a cause for concern. They also did not detect Lloviu virus in samples of almost 1,300 healthy bats.

Bats have important roles in plant pollination, spreading plant seeds and controlling insect populations, and pathogens that attack bat populations could have dramatic ecological and health-related consequences.

"The Lloviu virus discovery highlights how much we still need to learn about the world of emerging infectious diseases and the importance of global collaboration and the One Health initiative in addressing the challenge," said CII Director Dr. Ian Lipkin.

**Human Norovirus in Groundwater Remains Infective After Two Months**

*ScienceDaily* (Oct. 20, 2011) — Researchers from Emory University have discovered that norovirus in groundwater can remain infectious for at least 61 days. The research is published in the October *Applied and Environmental Microbiology*.

Human norovirus is the most common cause of acute gastroenteritis. The disease it causes tends to be one of the more unpleasant of those that leave healthy people unscathed in the long run, with diarrhea
and vomiting that typically last for 48 hours. Norovirus sickens one in 15 Americans annually, causing 70,000 hospitalizations, and more than 500 deaths annually, according to the Centers for Disease Control and Prevention.

The results answer a question of great importance to public health, which had driven researcher Christine Moe and her colleagues to conduct this research: If well water becomes contaminated with noroviruses—perhaps from leaking sewer lines or a septic tank—how long do these noroviruses survive in water, and when would it be safe to drink from that well?

To answer that question, they prepared a safety-tested virus stock solution. They then put a known amount of this solution into a container of groundwater from an Atlanta well, which had met Environmental Protection Agency drinking water standards.

The researchers then tested the virus infectivity at days naught, 4, 14, 21, 27, and 61, by having volunteers drink the water on those days. The durability of the virus' infectivity was unexpected, says Moe. Most of the 13 volunteers became infected at various time points, exhibiting among them the complete range of norovirus symptoms, which endured for as long as five days post challenge. "We were surprised to observe that even the volunteers that drank the water 61 days after we had added the virus still got infected with the norovirus," says Moe.

Norovirus may remain infective far longer than 61 days. The researchers stored the groundwater at room temperature in the dark, using reverse transcription polymerase chain reaction to determine how much viral RNA remained after 622 days, and again after 1,266 days. They found no reduction after the first interval, and very little at the end of the second interval. Unfortunately, funding was insufficient to test infectivity in human volunteers beyond day 61.

"This study provides further evidence of the need to treat groundwater used for drinking water," says Moe, adding that the Environmental Protection Agency and other decision-makers who regulate drinking water need to take these findings into account, particularly since roughly half the US population relies upon groundwater for drinking.

To ensure that the volunteers' health would not be compromised, the investigators conducted the study in a special research unit of Emory University Hospital, while taking a variety of other precautionary measures.

Anticipating a question about who would volunteer to participate in a study with such potentially unpleasant consequences, Moe says that some volunteers have said that "they want to see how good their immune system is, and whether they will actually get sick." Three of the 13 volunteers did not become sick. One volunteer was the local librarian "who came to the research unit with a huge bag of books that she wanted to read while she was in the study," says Moe.

**Journal Reference:**

'High viral load' should mean over half a million copies, not over 100,000, Rome study suggests
Gus Cairns
Published: 24 October 2011

A study by the University of Rome has found that a substantial proportion of patients with HIV are being diagnosed with viral loads of over half a million copies/ml, and it is these patients who are at raised risk of treatment failure when they begin antiretroviral therapy, rather than patients with viral loads over the conventional 'high' threshold of 100,000 copies/ml.

Professor Carlo Perno told the 13th European AIDS Conference (EACS) that the average viral load in a cohort of 1430 patients starting antiretroviral therapy between 2006 and 2009 was in fact 125,000 copies/ml. The average CD4 count was 202 cells/mm³.

The study found that the most popular first-line treatment regimens were tenofovir/FTC/boosted lopinavir (Truvada/Kaletra) and tenofovir/FTC/efavirenz (Atripla): using protease inhibitors in first-line treatment is more popular in Italy than the United Kingdom.

Professor Perno divided the patients into strata according to their viral load on starting treatment and found that roughly a quarter of patients each had viral loads below 30,000 copies/ml (30K); between 30K and 100K; and between 100K and 300K. Ten per cent had viral loads between 300K and 500K and 15% over 500K.
For the entire cohort the median time taken after starting therapy to reach a viral load below 50 copies/ml was 18 weeks, with 90% virally suppressed by week 48. This rate of viral suppression was on an intention-to-treat analysis, which included people changing therapy for non-virological reasons, stopping therapy or being lost to follow-up. In an on-treatment analysis restricted to people staying on their first-line therapy, the average time to 50 copies/ml was 16 weeks and 94% were virally suppressed by week 48. The average time to a viral load below 50 copies/ml and the percentage undetectable at week 48 was as follows for the five viral load strata, on an on-treatment analysis:

<table>
<thead>
<tr>
<th>Viral load</th>
<th>Time to 50 copies/ml</th>
<th>Below 50 copies/ml at week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 30K</td>
<td>10 weeks</td>
<td>99%</td>
</tr>
<tr>
<td>30-100K</td>
<td>15 weeks</td>
<td>98%</td>
</tr>
<tr>
<td>100-300K</td>
<td>18 weeks</td>
<td>93%</td>
</tr>
<tr>
<td>300-500K</td>
<td>22 weeks</td>
<td>93%</td>
</tr>
<tr>
<td>Over 500K</td>
<td>23 weeks</td>
<td>84%</td>
</tr>
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</table>

Compared with patients with pre-treatment viral loads under 30,000 copies/ml, the patients in the other four viral load strata were respectively 40%, 64%, 64% and 77% more likely to fail to achieve viral loads under 50 copies/ml at week 48.

One in ten patients with pre-treatment viral loads over 500,000 copies/ml who had achieved a viral load under 50 copies/ml by week 24 of treatment subsequently rebounded, compared with 5.4% with viral loads between 30,000 and 500,000 and 3.1% with viral loads below 30,000 copies/ml.

Professor Perno commented: “Patients with viral loads over 500,000 copies/ml represent a significant population, at higher risk of virologic failure and rebound, that may deserve special attention, and a selected therapeutic approach.” He suggested that the concept of 'high viral load' needed to be revised.

Reference
Perno CF et al. High pre-therapy viral load is associated with delayed and decreased control of HIV replication also at the time of modern HAART. Thirteenth European AIDS Conference, Belgrade, abstract PS11/5, 2011.

Lung cancer is biggest killer in study of non-AIDS-defining cancers
Gus Cairns
Published: 22 October 2011
A large cohort study of non-AIDS-defining cancers in people with HIV has found that while lung cancer was responsible for 16% of cases of these cancers it was responsible for 37% of non-AIDS-defining cancer deaths. Anal, liver, prostate and head and neck cancers and Hodgkin's lymphoma were also common but without lung cancer's high mortality rate.

The D:A:D study is a major cohort study of 35,000 patients in Europe, the US and Australia and has previously been responsible for a wealth of data on drug side-effects and conditions like diabetes and cardiovascular disease.

This study collected cases of, and deaths from, non-AIDS-defining malignancies (NADMs—cancers) from eight out of eleven national cohorts in D:A:D between the start of 2004 and the end of January 2010. NADMs include all cancers except the AIDS-defining ones which are the most strongly related to low CD4 counts: Kaposi's sarcoma, cervical cancer and non-Hodgkin's lymphoma.

The study found 880 NADMs altogether, representing an incidence of one NADM diagnosed per 200 patients a year. Eighty per cent of cases were men partly because there are more men than women in the D:A:D cohort but also because men were 52% more likely to develop NADMs. The average latest CD4 count of cases was 327 CD4 cells/mm³ and the median lowest-ever count 127 CD4 cells/mm³; the vast majority were on antiretrovirals and the median viral load was 50 copies/ml, though 25% had viral loads over 250 copies/ml. One-third of the cohort were smokers.

The most common cancer was lung cancer with an incidence of one case per 1000 patients a year: anal cancer, the third most common, was roughly half as common as this. Annual incidence did not change over the six years of the study, except for a suggestion that the second most common cancer, Hodgkin's lymphoma, may have become slightly less so, with incidence changing from roughly one case per 1500 patients a year to one per 2000 in the last two years of the study.

Lung cancer was by some way the most lethal malignancy, with 80% of diagnosed patients dead within 2.5 years: the death rate for lung cancer was 2.3 times the rate for all NADMs. In contrast Hodgkin's lymphoma and anal cancer had half the average death rate of all NADMs, and in the case of Hodgkin’s, 25% of patients died not necessarily of the cancer) within the next two years but there were few deaths thereafter.
In multivariate analysis, being an ex-smoker raised the risk of death due to NADMs by 66%. Being a current smoker was associated with a 28% raised risk of NADM-related death, and this was not statistically significant, but this is likely due to current smokers having a raised death rate for other reasons, such as cardiovascular disease, as well as lung cancer.

Being male raised the NADM mortality risk by 52% and having been an injecting drug user by 59%. For each year longer patients had been diagnosed with HIV, their NADM-related death rate increased by 9% and by 5% for every 50 fewer CD4 cells/mm³. Age (an 11% raised risk per five years older) and hepatitis C infection (a 28% increased risk) were of borderline significance in relation to ADM mortality.

Reference

HIV couple 'bit officers after refusing to stop having sex in public pool'
Lucasz Rutkowski and Tanya Kalonga are charged with attacking police officers at a leisure centre in Edinburgh.
24 October 2011 14:27 BST
An HIV positive couple are alleged to have attacked police officers after refusing to stop having sex in a public swimming pool.
The couple allegedly spat at and bit officers after police ordered them out of the pool at the Ainslie Park Leisure Centre in Pilton, Edinburgh.

According to papers lodged at the city's sheriff court, Lucasz Rutkowski and Tanya Kalonga have been charged in relation to the August 9 incident.
The couple face claims they "engaged" in "sexual activity" and "appeared" to "have sexual intercourse within a public swimming pool".

Rutkowski and Kalonga are alleged to have repeatedly refused to leave the pool when asked to do so by police officers and struggled violently with them.

Rutkowski is charged with spitting at and biting Constable Craig Reid of Lothian and Borders police to his injury, while knowing he was HIV positive.
The 23-year-old is also said to have attacked another constable Derek Neish.
A charge claims he "did lash out with your arms and legs, struggle violently on the ground whilst you were bleeding, and said Derek Neish was bleeding, knowing you were HIV positive".

Rutkowski is also charged with striking his head against, and spitting all over, the cage of a police van. He is also alleged to have called Constable Andrew Kendall a "Scottish p***" and a "racist p***".
Kalonga is accused of attempting to rescue Rutkowski by trying to pull Constable Reid away from him. She is also said to have injured Constable Reid by scratching his arms and spitting at him, while knowing she was HIV positive.
The 21-year-old is also accused of spitting at another officer Christine Gray and a man called John Kenny with the knowledge she had the disease.
Both Rutkowski and Kalonga are also accused of threatening to shoot Mr Kenny and his family during the alleged incident.
The case is due to call for a first diet at Edinburgh Sheriff Court on November 8 and a trial has been set for November 21.

Epidemiological Impact of Tenofovir Gel on the HIV Epidemic in South Africa
Journal of Acquired Immune Deficiency Syndromes Vol. 58; No. 2: P. 207-210, (10.01.2011) Brian G. Williams, PhD; Salim S. Abdool Karim, MBChB, PhD; Quarraisha Abdool Karim, PhD; Eleanor Gouws, PhD
In a previous randomized controlled trial in South Africa, a tenofovir-based vaginal microbicide gel reduced HIV acquisition in women by 39 percent. To better inform policy, the current study assessed the population-level impact of this antiretroviral-based gel on HIV incidence, prevalence and deaths, and cost-effectiveness, using a dynamic model of HIV transmission calibrated to South Africa's epidemic.
The results showed that if used by women in 80 percent or more of sexual encounters (high coverage), the gel could prevent 2.33 (0.12 to 4.63) million new infections and save 1.30 (0.07 to 2.42) million lives over the next 20 years. A lower coverage, use of the gel in only 25 percent of sexual encounters, could avert 0.50 (0.04 to 0.77) million new infections and save 0.29 (0.02 to 0.44) million lives over the next 20 years.
At $0.50 per application, the cost per HIV infection prevented at low coverage would be $2,392 ($562 to $4,222), and the cost per disability-adjusted life year saved would be $104 ($27 to $181). High coverage would cut these costs by about 30 percent.

“Over 20 years, the use of tenofovir gel in South Africa could avert up to 2 million new infections and 1 million AIDS deaths,” the study authors concluded. “Even with low rates of gel use, it is highly cost-effective and compares favorably with other control methods. This female-controlled prevention method could have a significant impact on the epidemic of HIV in South Africa. Programs should aim to achieve gel use in more than 25 percent of sexual encounters to significantly alter the course of the epidemic.”

When Alienated by Past Providers, LGBT Patients Are Often Reluctant to Seek Medical Care

*Boston Globe*, (10.10.2011) Neena Satija

Researchers say STDs are among the health problems LGBT people are more likely to experience than their heterosexual peers. One key reason is that fear of or experience of stigma from their provider keeps many LGBTs from seeking health care. Doctors could help by asking better questions, LGBT-competent providers say.

In getting to know transgender patients, a provider can ask, "How do you like to be called?" suggested Dr. Carole Allen, chief of pediatrics at Harvard Vanguard Medical Associates. Such an approach is important in speaking with adolescents who may be questioning their sexual orientation or gender, Allen said.

“As soon as you say to a patient, ‘Do you have a girlfriend?’ you’ve automatically cut off that conversation,” said Allen. About 10 years ago, Allen began asking “Have you noticed any attraction to boys or girls or both?”

“Some kids will laugh,” said Allen. “But I’ve heard some kids say, ‘I haven’t decided’ or ‘I don’t know.’” Some youths had not talked about their sexuality with anyone else. Allen helps link confused kids to the services they need and can talk about relevant safe-sex practices.

“It’s not necessarily what people say, it’s sort of what they don’t say,” said Tina Gelsomino, an administrator at Brigham and Women’s Hospital and co-chair of an LGBT staff group. Patient intake forms, for instance, rarely have space for patients to disclose their sexual orientation or transgender identity.

“Imagine how you would feel if you have an illness ... and you’re going to somebody [for health care] where you have to explain it to them,” said Joanne Herman, who underwent a sex-change operation in 2003. Herman said her previous doctor could not provide a gynecological exam without mentioning her lack of a cervix. Now at Boston’s Fenway Health, “my primary care doctor does my GYN exam, and it’s done without commentary,” she said.

Global Polio Eradication Initiative Not On Track To End Transmission by 2012, Report Says

The latest quarterly *report* (.pdf) by an independent board that monitors the progress of the Global Polio Eradication Initiative (GPEI), released in mid-October, warned that "unless the program addresses 'fundamental problems,' there is a 'substantial risk' that stopping polio transmission will not be achieved by end-2012," AlertNet reports. "'Important changes in style, commitment and accountability are essential,' the panel of international health experts said," according to AlertNet, which adds, "Afghanistan, India, Nigeria and Pakistan are still classified as 'polio-endemic,'" and "in Angola, Chad and Democratic Republic of Congo, transmission has become re-established for 12 months or more."

GPEI—which includes the WHO, the CDC, the Bill & Melinda Gates Foundation and UNICEF—"has warned that insufficient funding at this stage would jeopardize the entire eradication effort," and "[t]he initiative ... faces a funding gap of $535 million, according to its website," AlertNet notes (Rowling, 10/21). The board writes in the report that GPEI is "not wholly open to critical voices, perceiving them as too negative—despite the fact that they may be reporting important information from which the program could benefit," Wired Magazine’s "Superbug" blog writes (McKenna, 10/22). The report release coincides with World Polio Day, observed on October 24, according to a Gates Foundation *press release*, in which the foundation calls for "increased commitment and greater accountability from political leaders to end polio, and for supporters around the world to lend their voices to the fight" (10/24).
UNICEF Warns Of Possible Polio Resurgence In Madagascar Amid Outbreak Involving Three Children

"An outbreak of polio in three children from the south of Madagascar has raised concerns over a possible resurgence of this crippling disease," BBC News reports, adding, "UNICEF spokesman Daniel Timme says three cases of polio without symptoms have been identified ... during UNICEF's Mother and Child Health week following tests and urine samples" (Healy, 10/22). "Although the children are currently not showing symptoms of polio, [Timme] said symptoms of the disease could make itself known at any time" Examiner.com writes (Herriman, 10/22).

According to BBC, "Polio vaccination programs must reach at least 80 to 90 percent of the population of the region to be effective," but "[s]hortages of fuel for refrigerators to store the vaccines, and the closure of 250 clinics, have reduced vaccination rates to less than 40 percent in the south" of the country. "Two further vaccination campaigns are now required to ensure 90 percent of the 700,000 children are vaccinated to curb a potential epidemic," the news service notes (10/22).

India Polio Free For 9 Months, Raising Hopes Of Eradication, Health Experts Say

"India has not had a case of polio in nine months, raising hopes the country is on the verge of defeating the disease, health officials said Monday," the Associated Press reports. "India remains one of only four countries in the world where polio is still endemic, and the nine months that it has been without a case is the longest since eradication efforts were launched nearly two decades ago," the AP writes, adding, "A country is declared polio free when no cases of the disease are reported for three years, according to the World Health Organization."

"India's success has followed 'persistent efforts over the last few years in the highest-risk areas and in reaching the most vulnerable populations, such as newborns, migrants and mobile populations,'" Health Minister Ghulam Nabi Azad said, according to the news service. "The government is aware, however, that a slip could lead to a resurgence of the disease," and "Azad said an immunization campaign continues in all high-risk areas and any new case would be declared a public health emergency," the AP adds (10/24).

Number Of Cholera Cases To Reach 500,000 By Year's End, WHO Says

The WHO on Friday "said the number of cholera cases in Haiti is expected to reach 500,000 by the end of the year" if current trends continue, Agence France-Presse reports. As of October, the agency estimated 470,000 cases of the disease and 6,600 cholera deaths had occurred since the outbreak began in 2010, the news service notes. "The number of new cholera cases in Haiti halved in August, but the rainy season is once again worsening the situation, the WHO warned," AFP writes (10/22).

"WHO cholera expert Claire-Lise Chaignat told reporters in Geneva on Friday that the disease was also likely to become endemic in the Caribbean nation," and said the WHO is determining the feasibility of a large-scale cholera vaccination campaign in Haiti, the Associated Press/Washington Post reports (10/21).

MSF Suspends Measles Vaccination Campaign In Mogadishu Area Because Of Violence

Medecins Sans Frontieres (MSF) last week cut short a three-week measles vaccination campaign intended to reach 35,000 children in the Daynile area near the Somali capital Mogadishu, after intense fighting erupted between the militant group al-Shabab and forces of Somalia's Transitional National Government, backed by the African Union Mission in Somalia, VOA News reports. Only 4,831 children had been reached in six days, according to the news agency.

"The head of [MSF's] programs in Somalia, Duncan McLean, says measles combined with malnutrition is the main cause of death among children in Somalia. He says the suspension puts children in the Daynile area at grave risk," VOA writes (Majtenyi, 10/23). According to an MSF press release, "MSF continues to work in the Daynile hospital and in Mogadishu, where our teams provide medical and nutritional assistance to displaced populations" (10/21).
**Tenofovir Gel Confirmed To Be Effective Against Herpes In Lab Experiment, Study Shows**

Data from lab experiments published online by the journal Cell Host and Microbes last week show that the gel form of the antiretroviral tenofovir, which is being investigated as an HIV prevention method, works to inhibit the reproduction of herpes virus in tonsil and cervical tissue, the [New York Times](http://www.nytimes.com) reports.

The study was conducted to help confirm findings from a Centre for the AIDS Programme of Research in South Africa (CAPRISA) clinical trial released last year at the International AIDS Conference in Vienna that showed the gel reduced the risk of HIV infection among women who used it by 39 percent and the risk of contracting herpes by 51 percent, according to the newspaper. The latest study was performed by researchers from NIH, Gilead Sciences Inc. and universities in Belgium and Italy, the Times notes (McNeil, 10/20).

**Challenging The View That The World’s Growing Population Represents Power, Prosperity**

As the world’s population approaches seven billion, Joel Cohen, a mathematical biologist and the head of the Laboratory of Populations at Rockefeller University and Columbia University, examines the implications of “the enormous increases in households, cities, material consumption and waste” on health, agriculture, water security, the environment and poverty in this [New York Times opinion piece](http://www.nytimes.com). He writes, “For some in the West, the greatest challenge—because it is the least visible—is to shake off, at last, the view that large and growing numbers of people represent power and prosperity.”

"Today, while many people reject the equation of human numbers with power, it remains unpalatable, if not suicidal, for political leaders to admit that the United States and Europe do not need growing populations to prosper and be influential and that rich countries should reduce their rates of unintended pregnancy and help poor countries do likewise," he writes. "Henceforth we need to measure our growth in prosperity: not by the sheer number of people who inhabit the earth, and not by flawed measurements like GDP, but by how well we satisfy basic human needs; by how well we foster dignity, creativity, community and cooperation; by how well we care for our biological and physical environment, our only home," he concludes (10/23).

**Viruses Coaxed to Form Synthetics With Microstructures Akin to Those of Corneas, Teeth and Skin**

[ScienceDaily](http://www.sciencedaily.com) (Oct. 20, 2011) — Using a simple, single-step process, engineers and scientists at the University of California at Berkeley recently developed a technique to direct benign, filamentous viruses called M13 phages to serve as structural building blocks for materials with a wide range of properties.

By controlling the physical environment alone, the researchers caused the viruses to self-assemble into hierarchically organized thin-film structures, with complexity that ranged from simple ridges, to wavy, chiral strands, to truly sophisticated patterns of overlapping strings of material—results that may also shed light on the self-assembly of biological tissues in nature.

Each film presented specific properties for bending light, and several films were capable of guiding the growth of cells into structures with precise physical orientations.
Led by University of California at Berkeley bioengineer Seung-Wuk Lee and his student and lead author Woo-Jae Chung, the researchers published their findings in the Oct. 20, 2011, issue of *Nature*.

“We are very curious how nature can create many diverse structures and functions from single structural building blocks, such as collagens for animals and celluloses for plants,” says Lee. “We have thought that periodic changes in cell activity—such as from day to night, or summer to winter—cause cells to secrete different amounts of macromolecules into confined and curved micro-environments, which might play critical roles in the formation of such sophisticated structures. We believe that biological helical nanofiber structures play a critical role in that process, yet for collagen and cellulose, it has proven quite difficult to engineer their chemical and physical properties to study their assembly process. Therefore, we have been looking for new, helical engineering materials.”

The fundamental unit of the novel films is the bacteria-hunting virus, M13. In nature, the virus attacks *Escherichia coli* (*E.coli*), but in bioengineering laboratories, the virus is emerging as a nanoscale tool that can assemble in complex ways due to its long, slender shape and its chiral twist.

"Fortunately," adds Lee, "M13 also possesses an elegant helical surface that makes it a best fit for this study."

In the Berkeley laboratory, the viruses are suspended in a buffered salt solution, into which the engineers dip a thin substrate onto which the viruses can adhere. By varying the speed at which they withdrew the substrates from the virus-rich solution, the concentration of viruses in the solution, and the ionic concentration, the researchers were able to craft three distinct categories of films.

The simplest film consisted of alternating bands of filaments, with the viral filaments in each band oriented perpendicular to the filaments in the adjacent band. Created using a relatively low concentration of viruses in the starter solution, the bands formed as the substrate rose out of the liquid with a repeated stick-slip motion.

To create films at the next hierarchical level of complexity, the researchers increased the concentration of viruses in the solution, which added more physical constraints to each filament’s movement within its environment. As a result, the filaments bunched together into helical ribbons, with a handedness at a broader scale than the handedness of each individual virus.

With even higher concentrations-and in some experiments, greater substrate-pulling speed-the withdrawal yielded ever more complex, yet ordered, bundles of filaments that the researchers referred to as "ramen-noodle-like."

"Nature can dynamically change environmental variables when building new tissues to control an assembly process," adds Chung, the first author. "The beauty of our system is that we can do the same. By altering various parameters we drive assembly towards specific structures in a controlled manner. We can even make different structures on the same substrate."

By varying their techniques, the researchers altered the physical environment for the viral filaments, ultimately forcing the viruses to align into the highly specialized structural films. Each film is different, as expressed by differences in color, iridescence, polarity and other properties.

In one expression of those differences, structures built using faster-pulled substrates yielded patterns that reflected ever-shorter wavelengths of light—50 microns per minute yielded material that reflected light in the orange color range of the spectrum (600 nm), while 80 micrometers per minute yielded blue light (450 nm). The process was precise, allowing the researchers to tune the films to various wavelengths and colors, and induce polarization.

The researchers believe the hierarchical nature of the structures reflects the hierarchical growth patterns of similar biomolecules in nature, processes that result in chiral materials, like collagen, expressing themselves as the building blocks of a cornea in one level of self-assembly and the building blocks of skin tissue at a more complex level. Such self-assembly yields stunning macroscale structures—for example, skin tissue that appears blue on birds and blue-faced monkeys is actually not expressing the light absorption from blue pigment, but the blue light scattered by complex arrays of chiral, molecular building blocks.

"We strongly believe that our novel approach to constructing biomimetic 'self-templated', supramolecular structures closely mimics natural helical fiber assembly," says Lee. "One important reason is that we not only mimicked the biological structures, but we also discovered structures that have not been seen in nature or the laboratory, like the self-assembled 'ramen-noodle structures' with six distinct order-parameters."

In addition to crafting novel biomolecular films with unique traits, the researchers also demonstrated that the films can serve as biological substrates. The team was able to grow sheets of cells that were
 oriented based on the texture of such substrates, with one variation incorporating calcium and phosphate to create a biomaterial similar to tooth enamel.

"This novel, self-templating, biomaterials assembly process could be used in many other organic and inorganic materials to build hierarchical structures to tune optical, mechanical and even electrical properties from nano to macro scales," adds NSF Biomaterials program director Joseph Akkara, who helped fund the project. "The reported approaches could be used to investigate mechanisms for diseases such as Alzheimer’s, which is caused by amyloid aggregation in our brain tissues. More broadly, the breakthroughs could potentially yield scientific impacts in the area of tissue regeneration and repair."

Journal Reference:

### Complexities of DNA Repair Discovered

ScienceDaily (Oct. 23, 2011) — An international team of scientists led by UC Davis researchers has discovered that DNA repair in cancer cells is not a one-way street as previously believed. Their findings show instead that recombination, an important DNA repair process, has a self-correcting mechanism that allows DNA to make a virtual u-turn and start over.

The study’s findings, which appear in the Oct. 23 online issue of the journal *Nature*, not only contribute new understanding to the field of basic cancer biology, but also have important implications for potentially improving the efficacy of cancer treatments.

"What we discovered is that the DNA repair pathway called recombination is able to reverse itself," said Wolf-Dietrich Heyer, UC Davis professor of microbiology and of molecular and cellular biology and co-leader of Molecular Oncology at UC Davis Cancer Center. "That makes it a very robust process, allowing cancer cells to deal with DNA damage in many different ways. This repair mechanism may have something to do with why some cancer cells become resistant to radiation and chemotherapy treatments that work by inducing DNA damage."

Heyer likens this self-correcting ability of the DNA repair system to driving in a modern city where u-turns and two-way streets make it easy to rectify a wrong turn. "How much harder would it be to re-trace your path if you were in a medieval Italian city with only one-way streets," he said.

In the current study, Heyer and his colleagues used yeast as a model system to elucidate the mechanisms of DNA repair. They expect their findings, like most that come out of work on yeast, will be confirmed in humans. "Whether in yeast or humans, the pathways that repair DNA are the same," Heyer said.

The research team used electron microscopy to observe repair proteins in action on strands of DNA. They saw a presynaptic filament called Rad51 regulating the balance between one enzyme (Rad55-Rad57) that favors recombination repair and another (Srs2) that inhibits recombination repair. By controlling the balance between the two enzymes, Rad51 can initiate genetic repair—or the u-turn—as needed.

"It is a tug-of-war that has important implications for the cell because, if recombination occurs at the wrong time in the wrong place, the cell may die as a consequence." The ability of the repair system to abort ill-fated repair attempts, gives the cell a second shot, improving cellular survival after its DNA is damaged. This is exactly what is dreaded in cancer treatment.

"There are a lot of hints in the scientific literature suggesting that DNA repair contributes to resistance to treatments that are based on inducing DNA damage such as radiation or certain types of chemotherapy," Heyer said. "The ability of cancer cells to withstand DNA damage directly affects treatment outcome, and understanding the fundamental mechanisms of the DNA repair systems will enable new approaches to overcome treatment resistance."

Heyer said the team's next step is to look at the enzyme system in humans and see whether they find the same principles at work. This work has received funding and has already begun. One application of this work will be to target the self-correcting mechanism in cancer cells as a way of sensitizing them to radiation and/or chemotherapy treatments.

"If we can confirm that these types of mechanisms exist in human cells, then we will have an approach for making cancer cells more sensitive to DNA damage-inducing treatments."

Journal Reference:
Jie Liu, Ludovic Renault, Xavier Veaute, Francis Fabre, Henning Stahlberg, Wolf-Dietrich Heyer. **Rad51 paralogues Rad55–Rad57 balance the antirecombinase Srs2 in Rad51 filament formation.** Nature, 2011; DOI: [10.1038/nature10522](https://doi.org/10.1038/nature10522)
Central Asia’s Hidden Burden of Neglected Tropical Diseases (long)
Peter J. Hotez1, Ken Alibek2

1 Sabin Vaccine Institute and the National School of Tropical Medicine at Baylor College of Medicine, and Texas Children’s Hospital, Houston, Texas, United States of America, 2 Nazarbayev University, Astana, Kazakhstan

The neglected tropical diseases (NTDs) are the most common infections of the world’s poorest people living in developing countries [1–7]. They are mostly comprised of chronic parasitic and related infections, with the most common NTDs represented by the soil-transmitted helminthiases, schistosomiasis, lymphatic filariasis, onchocerciasis, and trachoma [1]. Among their common features, the NTDs result in prolonged periods of disability and actually help to promote poverty through their long-standing effects on child development and worker productivity [2]. It is not commonly appreciated that the NTDs are widespread throughout Central Asia where they are also a major determinant of poverty [8].

The five mostly landlocked Central Asian countries—Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, and Uzbekistan (Figure 1)—were established upon the breakup of the former Soviet Union in 1991. They are also linked in history as a vital crossroads (“the Silk Road”) between Asia and Europe and by a common geography comprised of a desert and piedmont region [9]. The five nations have a combined population of 60 million people, with three of them—Kyrgyzstan, Tajikistan, and Uzbekistan—exhibiting a Human Development Index (HDI) that is ranked below 100, which is more or less equivalent to nations such as Guatemala, India, Indonesia, and South Africa [10].

Figure 1. Commonwealth of Independent States – Central Asian States.

During the Soviet era in the 20th century, some gains were made in parasite and NTD control. For instance, in Uzbekistan a number of NTDs were either eradicated or eliminated as a public health problem, including dracunculiasis in 1931, urban cutaneous leishmaniasis in 1950, malaria in 1960, visceral leishmaniasis in 1968, and hookworm infection in 1974 [11]. However, following the 1991 breakup of the Soviet Union, public infrastructures and services deteriorated in many areas of Central Asia, and breakdowns in health care and preventive services ensued [12]. Of particular relevance to zoonotic NTDs
and according to Torgerson et al., the Soviet breakup also meant that large mechanized slaughterhouses were closed, leaving livestock production in the hands of small farms and unsupervised homes, and largely without veterinary inspection [13], [14]. Together with increases in pet and security dogs, veterinary public health was compromised, with a resultant re-emergence of several important NTDs, including echinococcosis and possibly toxocariasis [13]. As a result, today several NTDs either remain widespread in Central Asia or may have even increased in prevalence over the last two decades. They include the soil-transmitted helminth infections, food-borne and zoonotic parasitic infections, and vector-borne protozoan infections (Table 1).

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence</th>
<th>Country Where Measured</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intestinal helminth infections</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascariasis</td>
<td>23%</td>
<td>Kyrgyz Republic (Osh oblast)</td>
<td>[12]</td>
</tr>
<tr>
<td>Enterobiasis</td>
<td>19%</td>
<td>Kyrgyz Republic (Osh oblast)</td>
<td>[12]</td>
</tr>
<tr>
<td>Hymenolepiasis</td>
<td>4%</td>
<td>Kyrgyz Republic (Osh oblast)</td>
<td>[12]</td>
</tr>
<tr>
<td><strong>Cystic echinococcosis</strong></td>
<td>Up to 30 cases per 100,000 (1% of population)</td>
<td>Kazakhstan, Kyrgyz Republic, Tajikistan, Turkmenistan, [13],[15]</td>
<td></td>
</tr>
<tr>
<td>Echinococcosis</td>
<td>1.2 million cases</td>
<td>Kazakhstan, Belarus, Ukraine, Western Siberia</td>
<td>[27]</td>
</tr>
<tr>
<td>Fascioliasis</td>
<td>2%</td>
<td>Kyrgyz Republic (Osh oblast)</td>
<td>[12]</td>
</tr>
<tr>
<td>Toxocariasis</td>
<td>11%</td>
<td>Kazakhstan (rural eastern)</td>
<td>[15]</td>
</tr>
<tr>
<td><strong>Vector-borne protozoan infections</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leishmaniasis (cutaneous L. major; visceral L. infantum)</td>
<td>Not determined</td>
<td></td>
<td>[35]-[37]</td>
</tr>
<tr>
<td>Malaria</td>
<td>Number of probable and confirmed:</td>
<td>Number of suspected cases:</td>
<td>[39]</td>
</tr>
<tr>
<td>Kyrgyzstan 4</td>
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<td>Kyrgyzstan 33,983</td>
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<tr>
<td>Tajikistan 165</td>
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<tr>
<td>Turkmenistan 0</td>
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<td>Uzbekistan 4</td>
<td></td>
<td>Uzbekistan 916,839</td>
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<tr>
<td><strong>Other protozoan infections</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>16% (seroprevalence)</td>
<td>Kazakhstan (rural eastern)</td>
<td>[15]</td>
</tr>
</tbody>
</table>

Table 1. Selected Neglected Tropical Diseases in Central Asia.

**Intestinal Helminth Infections**

The major soil-transmitted helminth infections in Central Asia include ascariasis and enterobiasis. Overall, these nematode infections are understudied in Central Asia. The most recent complete assessment of intestinal helminth infections was provided recently by Steinmann et al., who conducted a cross-sectional study of 1,262 children among 51 rural primary schools in southwestern Kyrgyzstan [12]. It was found that most of the children had at least one intestinal helminth infection, led by ascariasis (23%), enterobiasis (19%), and hymenolepiasis (4%). Noted among the risk factors for soil-transmitted helminth infections were the absence of sanitation (ascariasis), and poverty and sharing of beds (enterobiasis). In contrast, the availability of tap water and washing of raw vegetables mitigated the risk of infection [12]. In Uzbekistan, these infections have been responsible for losses in economic productivity [16]. Steinmann et al. make the case that Kyrgyzstan (and possibly elsewhere in Central Asia) would benefit from mass drug administration (MDA), possibly with a single dose of mebendazole, which is highly effective against both ascariasis and enterobiasis [17], in addition to health education programs and increased clean water availability [12].

**Zoonotic Helminth Infections**

The major Central Asian zoonotic helminth infections include echinococcosis, opisthorchiasis, and fascioliasis; toxocariasis and trichinellosis are also present.

**Echinococcosis**

A rise in the number of cases of cystic echinococcosis caused by *Echinococcus granulosus* has been noted since 1991 [8], [18], which Torgerson et al. attribute to the breakdowns in veterinary public health as outlined above [13]. Overall, cystic echinococcosis has increased 4- to 5-fold over the last two decades in four of the Central Asian nations and in parts of Kazakhstan [13]–[15]. Today, the incidence rates of infection approach 30 cases per 100,000 in some districts, although the disease is believed to be vastly underreported [13], [19]. Some areas may be considered hyperendemic—for instance, in a study in rural eastern Kazakhstan, approximately 1% of the population exhibited evidence of cystic echinococcosis by
ultrasound [15]. Another concerning trend is the disproportionate rise in pediatric cases [13]. Such observations are complemented by veterinary epidemiologic studies in dogs showing that 20% or more of dogs harbor adult E. granulosus tapeworms [20], with a high prevalence in both Kyrgyzstan and Kazakhstan [20, 21]. Russia has also experienced an increase in imported cases from Central Asia [22]. Alveolar echinococcosis is also prevalent both among dogs, rodents, and in definitive host red foxes [20, 23–25].

**Fluke Infections: Opisthorchis and Fascioliasis**

Globally, there are an estimated 1.2 million cases of opisthorchiasis caused by the liver fluke Opisthorchis felineus, which occur primarily in Western Siberia (the Ob and Irtysh River valleys), Ukraine, Belarus, and Kazakhstan [26]. In Kazakhstan, opisthorchiasis is endemic in Aktyubinsk, Dzhezkazgan, Karaganda, Pavlodar, Tselinograd, and Turgay districts [26]. The infection is transmitted by the ingestion of uncooked and sometimes salted fish known as stroganina [26], and O. felineus has been associated with co-infection with Helicobacter pylori [29]. O. felineus infection results in fever and hepatitis, leading to abdominal pain. Advanced cases also result in suppurative cholangitis, liver fibrosis, and ultimately cholangiocarcinoma. An estimated 400 cases of cholangiocarcinoma occur annually from chronic O. felineus infection [30]. Fascioliasis and dicrocoeliasis are also found in Central Asia, with an overall approximate prevalence of close to 2% among school-aged children in Kyrgyzstan [12].

**Toxocariasis and Trichinellosis**

Toxocariasis is prevalent in rural Kazakhstan, especially among children [15], and the infection may be common elsewhere in Central Asia. After Trichinella spiralis, Trichinella britovi is the second most common Trichinella species affecting humans and an important species in Central Asia [31]. T. britovi has a sylvatic life cycle with boars, horses, foxes, and jackals as animal reservoir hosts, although it can also infect domestic pigs [31]. Trichinella pseudospiralis is also prevalent [31]. There are no disease burden estimates for these species.

Pozio recently made recommendations to the European Union for the control of food-borne helminth infections [32], but they also apply to Central Asia. These recommendations include improvement of farming conditions with health education of livestock producers and farmers, increased efforts and improved methods to detect parasites in slaughtered animals, reductions in contact between livestock and wild animals, and control of sewage sludge on pastures [32].

**Vector-Borne Protozoan Infections**

The two major protozoan infections in Central Asia are leishmaniasis and vivax malaria.

**Leishmaniasis**

The two major forms of leishmaniasis are zoonotic cutaneous leishmaniasis (ZCL) and visceral leishmaniasis (VL). In Central Asia, ZCL is caused predominantly by Leishmania major, first described in 1914 by the Russian physicians Yakimov and Schokhor as L. tropica major from a patient in Uzbekistan [33]. Additional molecular typing has differentiated human L. major species (L. major sensu stricto) from the closely related animal species Leishmania turanica and Leishmania gerbilli [33]. Human ZCL occurs when humans enter sylvatic habitats in river valleys that interrupt the deserts and piedmont plains of Central Asia where both the great gerbil, Rhombomys optimus [34], and the Phlebotomus papatasi sandfly vector [33, 35] are found. In Uzbekistan, a highly aggressive form of ZCL from L. major has also been reported [36]. There are no prevalence estimates available for L. major ZCL in Central Asia. Leishmania infantum is the major cause of VL in Uzbekistan and Tajikistan. This strain of L. infantum is believed to be separate from a strain found in Europe, the Middle East, and North Africa [37].

**Malaria**

There is no endemic malaria in Kazakhstan, and in 2010 Turkmenistan became the first Central Asian country to become certified as free of endemic malaria following control efforts that date back to the 1920s [38]. Since the 1950s, only Plasmodium vivax has been present, with the last autochthonous case registered in 2004 [38]. Uzbekistan also reported zero cases for the first time in 2009 [39]. In contrast, Tajikistan and Kyrgyzstan still report endemic malaria [39]. In Tajikistan, 30% of the population was at risk for malaria in 2009 [39]; however, the number of cases is down considerably from a peak of 30,000 reported cases in 1997 [40] as a result of programs of indoor residual spraying and MDA of primaquine and other anti-malaria drugs in the years following a five-year civil conflict from 1992 to 1997 [40–42]. Almost all of the cases are a result of P. vivax infections that peak in August and September, and are transmitted primarily by Anopheles superstictus and Anopheles pulcherrimus in areas of cotton and rice field irrigation [40]. Children are disproportionately affected [43, 44], and the highest morbidity occurs in the southern Khation region that borders on Afghanistan [43]. The P. vivax epidemic there is very much fueled by human migrations from Afghanistan and a permissive climate [41]. In turn, human
migrations from Tajikistan thwart efforts to eliminate malaria in Uzbekistan. P. vivax is also the predominant malaria parasite in Kyrgyzstan. Ultimately, control and elimination efforts for P. vivax malaria infections in Central Asia will depend upon ongoing indoor residual spraying with insecticides and MDA with primaquine (except for patients with glucose 6 phosphate dehydrogenase deficiency). Such large-scale efforts are being supported by the Global Fund to Fight AIDS, Tuberculosis and Malaria. Success in eliminating malaria will also depend on international cooperation with Afghanistan.

Among the other vector-borne neglected infections that exist in Central Asia are plague, tularemia, tick-borne relapsing fever, Crimean hemorrhagic fever, tick typhus, and Q fever.

**Other NTDs**

Toxoplasmosis was noted to be prevalent in rural Kazakhstan, but the overall prevalence in the region is unknown. Brucellosis is an important bacterial NTD. Similarly, intestinal protozoan infections such as amoebiasis and cryptosporidiosis are common and represent opportunistic infections among patients with HIV/AIDS. Canine rabies is still present in the region. Clonorchosis (liver fluke) is unknown. Brucellosis is an important bacterial NTD.

**Concluding Remarks**

With some exceptions, such as the detailed knowledge on malaria in the region and cystic echinococcosis, and the burden of Central Asia’s NTDs in the English scientific literature. The dearth of information may reflect a general absence of surveillance efforts in the two decades following the breakup of the Soviet Union, in parallel with breakdowns in human and veterinary public health infrastructure in these countries, although our observation may also reflect the fact that much of this information may be contained in the Russian scientific literature, which we did not tap. Among the priorities are stepped-up surveillance activities for the major intestinal helminth infections, including ascariasis and enterobiasis, the major food-borne and zoonotic helminth infections, and leishmaniasis and other vector-borne NTDs. Also of importance would be efforts to learn more about non-vector-borne protozoan infections such as toxoplasmosis and intestinal infections, brucellosis, and rabies. Some of these activities would be greatly aided by increased international cooperation between the Central Asian republics and with Afghanistan, which could also launch efforts for MDA of affected populations with soil-transmitted helminth infections and malaria, and livestock and vector control for the zoonotic NTDs, and possibly the establishment of a new international research center for NTDs. The Global Fund to Fight AIDS, Tuberculosis, and Malaria might also consider how to best integrate NTDs into their control and elimination programs. The burden of NTDs appears to be high among the poorest people living in Central Asia, and there is an urgent need to tackle this problem using multidimensional approaches.

**References**

Cellular Origins of Giant Viruses?

The largest virus to be sequenced prompts researchers to consider whether giant viruses were once full-fledged living organisms.

By Cristina Luiggi | October 16, 2011

Floating in the coastal waters of Chile, a team of French researchers has discovered and isolated yet another giant virus: Megavirus chilensis. Ringing in at a whopping 1.3 million base pairs, the Megavirus genome is the largest viral genome to be sequenced to date. Encoding around 1,120 putative proteins—the viral genome lies well in the range of many bacterial genomes and has researchers once again scratching their heads over the evolutionary origins of such mega-scale viruses.

A comparison of the genomes of Megavirus and Mimivirus—the first giant virus discovered—led researchers to conclude that not only are they distant relatives that share a wide range of genes including those for DNA repair, transcription, and viral factory genes, but that they may have both descended from an ancestor with a much larger genome. In fact, the authors suggest that the common ancestor may have been a free-living eukaryotic cell—one of the very first eukaryotic organisms—evidenced by the similarity of some giant virus genes with their living eukaryotic counterparts, Ars Technica reports. "Giant viruses might thus be relicts of the first chapters of the history of life," Carl Zimmer wrote in a Discover blog post. Ed Rybicki, Virologist Collapse

The discovery of the Megavirus—and Mimivirus too—shows that the biology of our planet is still so vast, and so undiscovered, that the tyranny of the hypothesis is still not absolute; there is still room for "discovery science".

So unless "We think there are more big viruses out there" can be taken seriously as a hypothesis, discovery rules, OK!! At least, in the marine environment.

But seriously now: the important facts here are that Megavirus shares most—but definitely not all—its genome with Mimivirus, BUT at such a genetic remove (<50% identity for most proteins) that it is almost certainly a very distant relative. It has also NOT sourced most of its genes by horizontal gene transfer from cellular organisms, meaning that what it has is what it started with, by and large.

Which complicates our picture of where big viruses and cells came from—because these viruses are right at the base of the eukaryote family tree, and it is not at all clear which came first.

I do love discovery virology. Only they won’t give me enough money to go out and play too...

Malaria Vax Yields Promising Results

Data from the Phase III trial of a malaria vaccine breeds hope for immunization as a possible weapon against the dreaded disease.

By Bob Grant | October 18, 2011

An experimental vaccine reduced the risk of developing malaria by about 50 percent in 6,000 sub-Saharan African children when combined with existing interventions, such as the use of insecticide-treated bed nets, according to a new study published online today by the New England Journal of Medicine.

Officials and researchers collaborating on the project announced preliminary results from the Phase III clinical trial of the RTS,S malaria vaccine today (18 October) at a malaria meeting in Seattle. “We’re on track to make history with this vaccine trial,” Christopher Elias, president and CEO of the Seattle-based nonprofit PATH organization, which collaborated in the trial, said during the news conference.

Doctors at 11 sites spread across seven African nations administered three successive doses of the RTS,S vaccine to 6,000 children, aged 5-17 months. Monitoring the patients for up to 12 months the
researchers found that the children were 56 percent less likely to experience clinical symptoms of malaria, and 47 percent less likely to develop severe symptoms of the disease.

The RTS,S vaccine, created in the late 1980s by researchers in pharmaceutical giant GSK’s Biologicals division, uses a protein from an existing hepatitis B vaccine to fuse a surface protein, called circumsporozoite, from the malaria parasite that helps it invade human liver cells, where it matures, reproduces, and launches its attack on the body’s red blood cells. GSK’s proprietary adjuvant mixture strengthens the immune response provoked by the vaccine. Partners in the trial, which began in 2009, include the PATH Malaria Vaccine Initiative, the Bill and Melinda Gates Foundation, the Walter Reed Army Institute of Research, and several African research centers.

The results announced today support data from the Phase II efficacy trial published earlier this year in *Lancet Infectious Diseases*. “Today this collaboration is bearing more sweet fruit in the form of hard data,” said Elias.

The RTS,S vaccine trial continues in Africa, with results in the crucial 6-12-week-old infant age group expected by the end of 2012, and long-term efficacy data for all of the study’s 15,460 participants expected by the end of 2014. According to GSK CEO Andrew Witty, the vaccine could garner approval by appropriate regulatory authorities and a recommendation from the World Health Organization by 2015.

Witty added that GSK would strive to make the vaccine as affordable as possible, contributing an estimated $50-100 on top of the $300 million already spent on the project to make the RTS,S vaccine, which does require refrigeration in transit, available to African children on a wide scale. “These data bring us to the cusp of having the world’s first malaria vaccine, which has the potential to significantly improve the outlook for children living in malaria endemic regions across Africa,” he said during today’s conference.


**Comments**

The 50% reduction in the risk of developing malaria by this vaccine in 6,000 sub-Saharan African children when combined with existing interventions, such as the use of insecticide-treated bed nets and use of mosquito repellents, are not very encouraging results. Had the study put proper control, that is, a group with just insecticide-treated bed nets without vaccine and a group with none? I believe that if used properly and regularly, a group with just insecticide-treated bed nets and use of mosquito repellents will also fare at the same level (50% reduction) as this vaccine is doing in combination with nets.

**Brian Hanley**

An excellent question. The journalist should have cited this study for comparison. Stephen S. Lim, Nancy Fullman, Andrew Stokes, Nirmala Ravishankar, Felix Masiye, Christopher J. L. Murray, Emmanuela Gakidou. Net Benefits: A Multicountry Analysis of Observational Data Examining Associations between Insecticide-Treated Mosquito Nets and Health Outcomes. *PLoS Medicine*, 2011; 8 (9): e1001091 DOI: 10.1371/journal.pmed.1001091, "... The pooled relative reduction in parasitemia prevalence from random effects meta-analysis associated with household ownership of at least one ITN was 20%." "... Sleeping under an ITN was associated with a pooled relative reduction in parasitemia prevalence in children of 24%." "... Ownership of at least one ITN was associated with a pooled relative reduction in mortality between 1 month and 5 years of age of 23%." "Our findings across a number of sub-Saharan African countries were highly consistent with results from previous clinical trials." These figures suggest that, standalone, the vaccine’s efficacy is in the range of 25%–30%. The problem with your control suggestion is that it is not ethical to remove, or to not supply, a known intervention that works for a deadly disease when testing something that is not known to be highly efficacious. The study designers did the right thing. rvspawaiya Collapse

Thanks Brian for your nice explanation. I have read the article suggested by you and agree with your estimate that effective vaccine’s efficacy is in the range of 25%-30%. I also agree with that ethical issue for using control with no ITN. These things are not actually possible when human beings are involved in the study. So all-in-all, a partially effective vaccine but a significant step towards malaria prophylaxis nonetheless.

**Bird Flu Vax Spurs Virus Evolution**

Inadequate poultry immunization programs may cause higher mutations rates in the bird flu virus, rendering the vaccine ineffective and increasing the threat of cross-species transmission.

By Edyta Zielinska | October 21, 2011
The H5N1 Type A influenza, commonly known as bird flu, is mutating faster in countries that have been implementing wide-scale, but incomplete, vaccinations of poultry, according to a report published online in Vaccine (October 12). The genetic changes accrued by the viruses rendered the vaccinations ineffective, and increased the risk that the virus could jump to humans.

That spotty vaccination campaigns seem “to favor viral mutation, has been suspected for a long time, but this is the first study which is providing hard evidence for it,” Marisa Peyre, a researcher with the French Agricultural Research Center for International Development who was not involved in the research, said in an email.

Bird flu has plagued poultry farmers for years, wiping out entire stocks, and occasionally jumping to the farmers themselves. In 2006, for example, the disease caused 79 human deaths worldwide. That same year, Egypt implemented wide-scale immunization programs against the virus, treating millions of farmed poultry with an H5N1 vaccine. Recent news, however, suggested that such programs were failing, with regular reports of bird and human infections. But it was unclear whether the failure was “caused by the vaccine cold-chain being broken”—thus rendering the vaccine ineffective—or if the virus was changing in a way that allowed it to infect even immunized animals, said first author Giovanni Cattoli, a veterinary scientist at the Istituto Zooprofilattico Sperimentale delle Venezie in Italy.

So Cattoli and colleagues, sequenced flu samples collected between 2006 and 2010 in countries that had vaccinated their poultry (Egypt and Indonesia), and compared the sequences to samples from countries that had no immunization programs in place (Nigeria, Turkey, Thailand). The results showed that the viruses circulating in countries with mass vaccination efforts were evolving faster, and had become genetically distinct from the virus that the vaccine was designed to combat. “There are sharp increases in genetic diversity of the virus,” said Cattoli.

Cattoli suspects that the problem stems from the way the vaccine was administered. Just as antibiotic-resistant strains of bacteria arise when antibiotics are not taken properly, evolution rates were likely to be higher in areas where the vaccination was incomplete, covering only a fraction of the chicken population. In addition, if vaccines can result in partial immunity if the vaccine is left out in the sun where its components decay, or if follow-up booster shots are not administered. In such cases, the chicken may not mount a strong enough immune reaction to fight the live virus. Most likely, said Cattoli, the virus moved from an unvaccinated chicken to one that was partially immunized, to one that hadn’t been infected or vaccinated at all. “All of this continuous movement among different levels of immunity is likely to drive and force the evolution of the virus,” he said.

Indeed, when Peyre investigated the vaccination practices in Egypt, she found that in some areas as little as 30 percent of the vaccinated bird population was protected from infection. In addition to the risk this poses to the poultry industry, a faster-evolving virus increases “the threat of emergence of a novel strain which might be one day be more specific to human infection,” said Peyre.

Cattoli’s study, she said, “emphasizes the critical needs for improved surveillance strategies and field protocols” in these countries, which can be both labor intensive and expensive. For countries looking for a quick fix, vaccination “is not the simplest way,” Cattoli agreed. Although there are no easy alternatives, he said, it is clear that inadequate vaccination campaign can wreak more harm than good.

### Epigenetic Effects of Childhood

**Living conditions in early life can have lasting, widespread effects on DNA methylation.**

**By Cristina Luiggi | October 21, 2011**

Wealth, housing conditions, and the occupation of a person’s parents during childhood are associated with widespread differences in DNA methylation later in life, a new study led by a group of researchers from Canada and the UK found. Analyzing the blood samples of 40 people from the UK who were born in 1958, the researchers found over 6,000 gene control regions (including 1,252 gene promoters) that showed significant differences in DNA methylation patterns depending on the standard of living conditions during the subject’s childhood. In contrast, about half the methylation differences in gene promoters (545) were associated with living conditions during adulthood.

“The current research represents just a beginning because it cannot tell us precisely when in early life these epigenetic patterns arose or what the long-term health effects will be,” author Chris Power, Professor of Epidemiology and Public Health at the UCL Institute of Child Health said in a press release. The findings were published yesterday (October 20) in the *International Journal of Epidemiology.*
Chronicling AIDS activists’ darkest days
Harvard project collects an oral history

By Martine Powers

Testimonies from more than 100 activists are part of the ACT UP Oral History Project, and they will now be at the Harvard College Library through a $500,000 bequest. The ACT UP project’s arrival at the nation’s largest college library represents a move to diversify the institution’s holdings, as well as the start of a sweeping undertaking to store archives digitally and make them available online.

Innovative Transdermal Patch for Delivery of HIV Medicine ***

ScienceDaily (Oct. 25, 2011) — An innovative delivery method for human immunodeficiency virus (HIV) medications has been developed through use of a transdermal patch, the first of its kind to treat HIV. This research is being presented at the 2011 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting and Exposition in Washington, D.C., Oct. 23-27.

HIV is an ever-growing worldwide epidemic. According to the World Health Organization, in 2009 an estimated 33.3 million people worldwide were infected. The Centers for Disease Control estimated that in 2008, 1.2 million people age 13 and older were living with HIV in the U.S. Many of these individuals take up to 20 pills daily to keep their viral load low.

Lead researcher Anthony Ham, Ph.D., and his colleagues from ImQuest Biosciences in Frederick, Md., developed a transdermal patch which releases more than 96 percent of the HIV medication over the course of seven days. "As we enter the fourth decade of HIV/AIDS, this new delivery method will hopefully reduce the numerous pills most HIV patients have to take daily," said Ham. "Taking medicines regularly reduces symptoms in HIV patients and extends lives. The transdermal patch offers an easier option for patients to comply with their medication regimes as compared to current treatments."

This non-invasive patch also shows a potential economic advantage in terms of shipping costs as compared to pills or needles. With an estimated 15 million people living with HIV in developing countries and only 5.3 million people with access to treatment, this offers a more affordable and accessible way to address this unmet medical need.

IDSA: Young Adult HIV Patients in Hospital More Often

By Ed Susman, Contributing Writer, MedPage Today
Published: October 25, 2011

BOSTON—Adolescents and young adults, ages 17-24, who were perinatally infected with HIV (PHIV) appear to have increased hospitalization rates compared with younger PHIV patients, researchers suggested here.

PHIV youth had a hospitalization rate of 44.2 per 100 patient-years compared with a rate of 16.7 per 100 patient-years for children, 2 to 5 years of age, and a rate of 20.8 per 100 patients-years for children ages 6 to 16 years ($P=0.02$), said Stephen A. Berry, MD, PhD, from Johns Hopkins University in Baltimore.

"The older patients in this study are probably the ones who were treated with monotherapy and dual therapy when they were infants and young children, so they are destined to have virus that is harder to treat," Berry told MedPage Today during his poster presentation at the annual meeting of the Infectious Diseases Society of America.

"In addition, these are now adolescents who are out from under parental control and do things that ... can lead to a lack of compliance," Berry said.

Berry and colleagues performed a retrospective study of 445 children and young adults who were treated for perinatal HIV infection during the years 2001 to 2008 and compared hospitalization rates of the youngest children to the oldest cohort. The greatest hospitalization rate was among the children under the age of 2 at 70.2 per 100 patient-years.

Most of the hospitalizations were because of infections and the majority of those were non-AIDS defining infections. The older group recorded 17.4 non-AIDS defining infections per 100 patient-years compared with eight such infections among the 6- to 16-year-old group. AIDS defining infections occurred in nine per 100 patients-years in the older youth compared with three per 100 patients-years in the younger children.

Berry also pointed out that the older youth in the study have slightly lower rates of HIV suppression—the ability to reduce viral loads to undetectable levels using the 400 copies/mL assay—when
compared with the 6- to 16-year-old group. He suggested that those differences showed the impact of resistant virus and adherence to medication.

"These are people who have been on medications for many years and may be showing signs of disease fatigue," suggested Bobby Gupta, MD, an internist from Corona, Calif. "Disease fatigue can lead to adherence issues. These patients have a long way to go."

The research team identified perinatally-infected HIV patients from four geographically diverse pediatric HIV clinics within the HIV Research Network (Maryland, Oregon, Tennessee, Pennsylvania). Among the patients, 52% were girls, 78% were black, and 4% were Hispanic. The median follow-up time was eight years.

A model adjusted for race, gender, CD4 cell count, HIV RNA, and antiretroviral therapy use found higher incidence rate ratios (IRR) for hospitalization of PHIV youth ages 17 to 24, compared with those ages 2 to 5 and ages 6 to 16, in all years except 2001. The IRR per year for the 17- to 24-year-old was 0.94 (CI 0.83, 1.05) versus 0.87 (CI 0.74, 1.02) for the 2- to 5-year-olds and 0.88 (CI 0.82, 0.94) for the 6- to 16-year-olds.

Also, among PHIV youth, a CD4 cell count of less than 200 cells/μL was the only independent predictor of a higher hospitalization rate.

"Interventions to improve the health of perinatally-infected HIV youth are urgently needed," Berry said. "Further studies, which determine the relative impact of psychosocial versus HIV-related factors may help in designing such interventions. Studies should also address whether costs associated with medical care are a significant barrier because many perinatally-infected HIV patients may transition away from state children's health insurance programs upon reaching 18 years of age."

"We see similar situations with our older adolescents," commented Fatima Kakkar, MD, from the University of Montreal Hospital. "They don't want to take their drugs."

This is a real unknown area and we are not clear on how to treat these individuals," she told MedPage Today. "This study shows that we have to do a better job with these young patients."

**State Sen. Pam Galloway Pushes Abstinence Bill**

*Wausau Daily Herald*, (10.20.2011) Kathleen Foody

A new bill introduced by state Sens. Pam Galloway and Mary Lazich would roll back the Healthy Youth Act, a comprehensive sex education initiative passed last year to help reduce rates of STDs and pregnancy among young people.

Under the proposed legislation, Wisconsin school districts offering sexual health courses would no longer be required to teach about birth control. Instead, districts could choose to adopt an abstinence-only or a comprehensive curriculum, provided abstinence is taught as the preferred choice for unmarried students; instruction is given on parental responsibility and the socioeconomic benefits of marriage; and pregnancy, prenatal development, and childbirth are explained.

School districts would no longer be required to notify parents if human development instruction is not offered, and volunteer health care providers would not be permitted to teach these courses.

Galloway said the new bill is intended to return curriculum control to local school boards. “The Healthy Youth Act was a one-size-fits-all approach,” she said.

At a packed committee hearing on Oct. 19, critics of the measure said it will increase pregnancy and STD rates among teens.

**Commonwealth Urged to Tackle Homophobic Laws**

*Agence France Presse*, (10.25.2011)

Ahead of the Commonwealth Heads of Government Meeting (CHOGM) this week in Perth, leaders tasked with developing reform options for member nations said homophobia and laws that criminalize gay sex must be addressed.

Anti-gay statutes are still in force in 41 of 54 Commonwealth nations. “It’s a very special British problem. And the problem is it makes it very difficult to get messages about HIV out,” said Michael Kirby, a retired High Court judge and Australia’s representative on the Eminent Persons Group (EPG).

Kirby expects cultural and religious objections from member nations, mainly comprising former British colonies from Canada to Cameroon and from New Zealand to Nigeria. “But you need to remove the criminal laws, and that is what the [EPG] is suggesting for the CHOGM meeting,” Kirby said.

Though not every Commonwealth country actively prosecutes gays, the effect of punitive laws is the creation of an environment in which people are fearful about seeking help or advice, said Rob Lake,
executive director of the Australian Federation of AIDS Organizations. “When people are forced to hide, or cover who they are and what they do ... they are not the people who get the messages about prevention, get the messages about treatment,” he said. “And that’s one of the factors in these high rates in Commonwealth countries,” which are home to some 30 percent of the world’s population but 60 percent of HIV/AIDS cases.

CHOGM leaders also will debate whether the body should adopt a charter of common values and create an office of commissioner for democracy, rule of law, and human rights.

**Sexual Behaviors and Situational Characteristics of Most Recent Male-Partnered Sexual Event Among Gay and Bisexually Identified Men in the United States**


Fewer than half of the gay and bisexual men surveyed for the current study said their most recent male-partnered sexual event involved anal intercourse.

The researchers sought to document the sexual behaviors reported by gay and bisexual men and to describe the situational characteristics and participants’ evaluation of the events. “Recent nationally representative studies documenting event-level sexual behavior have included samples that are predominantly heterosexual, resulting in limited information on the sexual repertoire of gay and bisexual men,” the authors wrote.

The team used an Internet survey to collect data from 24,787 gay and bisexual men from 50 US states and the District of Columbia. The measures included items relating to sociodemographics, recent history of sexual behavior, situational characteristics, orgasm, and ratings of arousal and pleasure.

Respondents ranged in age from 18 to 87 with a mean age of 39.2 years. Most (79.9 percent) identified as homosexual. Ethnicities represented included white (84.6 percent), Latino (6.4 percent,) and African-American (3.6 percent).

Kissing a partner on the mouth was the most commonly reported behavior (74.5 percent), followed by oral sex (72.7 percent) and partnered masturbation (68.4 percent). Anal intercourse was reported by 37.2 percent of respondents; the highest level of participation in anal sex (42.7 percent) was reported by men ages 18-24.

The most common location for sex was the participant’s home (46.8 percent), with fewer men reporting locations including hotels (7.4 percent) and public places (3.1 percent). Most men (63.2 percent) said their most recent sexual event included five to nine different sexual behaviors.

“These data provide one of the first examinations of sexual behaviors during the most recent male-partnered sexual event among gay and bisexually identified men in the United States,” the authors concluded. “Findings from this study suggest that gay and bisexually identified men have a diverse sexual repertoire and that partnered sexual behaviors are not limited solely to acts of penile insertion.”

**Study: Obesity limits effectiveness of flu vaccines**

People carrying extra pounds may need extra protection from influenza.

New research from the University of North Carolina at Chapel Hill shows that obesity may make annual flu shots less effective.

The findings, published online Oct. 25, 2011, in he *International Journal of Obesity*, provide evidence explaining a phenomenon that was noticed for the first time during the 2009 H1N1 flu outbreak: that obesity is associated with an impaired immune response to the influenza vaccination in humans.

"These results suggest that overweight and obese people would be more likely than healthy weight people to experience flu illness following exposure to the flu virus," said Melinda Beck, Ph.D., professor and associate chair of nutrition at the UNC Gillings School of Global Public Health and senior author of the study.

"Previous studies have indicated the possibility that obesity might impair the human body’s ability to fight flu viruses. These new findings seem to give us a reason why obese people were more susceptible to influenza illness during the H1N1 pandemic compared to healthy weight people."

The study reports for the first time that influenza vaccine antibody levels decline significantly in obese people compared to healthy weight individuals. What’s more, responses of CD8+ T cells (a type of white blood cell that plays a key role in the body’s immune system) are defective in heavier people.

Researchers studied people at a UNC clinic who had been vaccinated in late 2009 with inactivated trivalent influenza vaccine, the common flu vaccine for that fall and winter season. Although obese,
overweight and healthy weight individuals all developed antibodies to flu viruses within the first month after vaccination, the antibody levels in the blood declined more rapidly in obese and overweight individuals over time.

About 50 percent of obese participants had a four-fold decrease in antibody levels at 12 months compared to one month post vaccination. However, less than 25 percent of healthy weight participants had a four-fold decrease in antibody levels.

Also, when study participants' blood samples were tested in the lab and exposed to a flu virus 12 months after vaccination, about 75 percent of healthy weight people's CD8+ T cells still expressed interferon-γ, an infection-fighting protein. However, only about 25 percent of obese patients' cells responded by producing the protein.

When vaccination fails to prevent flu infection, people must rely in part on their CD8+ T cells to limit the spread and severity of infection, said Patricia Sheridan, Ph.D., research assistant professor of nutrition and an author on the paper.

"If antibody titers are not maintained over time in the obese individuals and memory CD+ T cell function is impaired, they may be greater risk of becoming ill from influenza," Sheridan said.

Heather Paich, a doctoral student in Beck's lab, added: "The findings also suggest overweight and obese people are more likely to become sicker and have more complications. That's because influenza-specific CD8+ T cells do not protect against infection, but instead act to limit the disease's progression and severity of disease."

In 2005, Beck and her colleagues reported that obesity in mice impaired the animals' ability to fight influenza infections and increased the percent dying from influenza, compared to lean mice with the same infections. In 2010, her team showed that obesity seemed to limit the mice's ability to develop immunity to influenza, suggesting vaccines may not be as effective in obese and overweight as in healthy weight humans. Also, the fatality rate was higher in obese mice – none of the lean mice died, but 25 percent of the obese mice died.

"This latest study shows that obese people may have a similar impaired response to influenza vaccines as our mouse models did to influenza virus," Beck said. "We need to continue to study the effect of obesity on the ability to fight virus infections. Influenza is a serious public health threat, killing up to half a million people a year worldwide. As rates of obesity continue to rise, the number of deaths from the flu could rise too. We need to better understand this problem and to look for solutions."

For more information or a copy of the study, see: http://www.nature.com/ijo/index.html

Unraveling the Mysteries of the Natural Killer Within Us
ScienceDaily (Oct. 24, 2011) — Scientists have discovered more about the intricacies of the immune system in a breakthrough that may help combat viral infections such as HIV.

Co-led by Professor Jamie Rossjohn of Monash University and Associate Professor Andrew Brooks from University of Melbourne, an international team of scientists have discovered more about the critical role Natural Killer cells play in the body's innate immune response.

The findings were published in Nature.

Natural Killer cells are a unique type of white blood cell important in early immune responses to tumours and viruses. Unlike most cells of the immune system that are activated by molecules found on the pathogen or tumour, Natural Killer cells are shut down by a group of proteins found on healthy cells.

These de-activating proteins, known as Human Leukocyte Antigens or HLA molecules are absent in many tumours and cells infected with viruses, leaving them open to attack by the Natural Killer cells.

Natural Killer cells recognise the HLA molecules using an inbuilt surveillance system called "Killer cell immunoglobulin-like receptors" (KIR).

Using the Australian Synchrotron, the team determined the three dimensional shape of one of these key KIR proteins, termed KIR3DL1, which binds to a particular HLA molecule.

This pairing is known to play a role in limiting viral replication in people with HIV, slowing the progression of the disease to AIDS.

Professor Rossjohn said that better understanding the structure of KIR proteins may help to develop approaches to better utilise Natural Killer cells to combat viral infection.

"It is only possible to detect proteins, such as KIRs, using extremely high-end equipment. The use of the platform technologies at Monash and the Australian Synchrotron was absolutely essential to this project's success," Professor Rossjohn said.

Professor Brooks said the researchers would use these findings to investigate other KIR molecules.
"Since KIR3DL1 is only a single member of a much larger family of receptors, the study provides key insight into how Natural Killer cells utilise other members of this important family of receptors to recognise virus-infected cells and tumours," Professor Brooks said.

The five-year project involved international collaborations with researchers from the National Cancer Institute—Frederick, National Institute of Allergy and Infectious Diseases, National Institutes of Health and Cardiff University School of Medicine.

**Journal Reference:**

**HIV associated with an increased risk of cataract surgery**
Michael Carter
Published: 26 October 2011

HIV-positive patients are significantly more likely to undergo surgery to remove cataracts in the eye, according to Danish research published in *Clinical Infectious Diseases*. A low CD4 cell count before and after the initiation of antiretroviral therapy was associated with cataracts, but there was no evidence that any individual anti-HIV drug was associated with an elevated risk of the condition.

Cataracts are cloudy patches that develop on the lens of the eye, either as a result of ageing or as a long-term consequence of viral infections and inflammation affecting the eye. Long-term corticosteroid treatment may also raise the risk of cataract development.

The investigators suggest that cataracts may be one of the "diseases of ageing" associated with HIV. They add that doctors should be aware of the condition, "however, taking the level of excess risk into consideration, there seems to be no indication for special ophthalmic examinations for cataracts or changes in treatment strategies."

Advances in treatment and care have resulted in dramatic improvements in the life expectancy of patients with HIV. Nevertheless, the anticipated life span of HIV-positive patients is still shorter than that of the general population. This is partly because patients with HIV have an increased risk of so-called diseases of ageing – for example cardiovascular disease, kidney and liver problems, osteoporosis, and some cancers. The exact reasons for this are controversial, but could include immune suppression, the inflammatory effects of HIV, co-infections, life-style factors, and the side-effects of some antiretroviral drugs.

Cataracts are well recognised as a disease of older age, and Danish investigators wished to see if they occurred with greater frequency in HIV-positive patients than in the general population.

Their study sample included the 5315 patients in the Danish national HIV cohort. Each patient was matched with ten HIV-negative individuals of the same sex and a similar age from the general Danish population.

The investigators compared the incidence of cataract surgery between the HIV-positive and HIV-negative populations. They also conducted a series of analyses to see if there were any factors associated with cataract formation in the HIV-positive patients.

Three-quarters of the HIV-positive patients were men and their median age was 37 years. A total of 44,561 person years of follow-up were contributed by the HIV-positive individuals, and 555,902 person years by the control population.

Cataract surgery was performed on 90 (1.7%) HIV-positive patients and 718 (1.4%) of controls. Eye disease that can predispose an individual to cataracts was detected in 252 (5%) of the patients with HIV and 494 (1%) of the HIV-negative individuals.

Overall the investigators found a higher risk of cataract surgery in the HIV-positive population compared to the controls (IRR = 1.87%; 95% CI, 1.50-2.33). A CD4 cell count below 200 cells/mm³ was associated with an increased risk of cataract surgery, both before starting HIV treatment (IRR = 3.11; 95% CI, 1.26-7.63) and after starting such treatment (IRR = 4.74; 95% CI, 2.60-8.62).

Comparison with the HIV-negative controls showed that HIV-infected individuals treated with antiretroviral drugs and a CD4 cell count above 200 cells/mm³ also had a significantly increased risk of cataract surgery (IRR = 1.87; 95% CI, 1.46-2.39).

Nevertheless there was no evidence that any individual antiretroviral drug increased the risk of cataracts.
“This study found a higher risk of cataract surgery in HIV-infected individuals compared with a non-HIV-infected age- and sex-matched comparison cohort,” comment the investigators. “Although the risk of ocular disease predisposing to cataract is higher in HIV-infected individuals, we found the risk of cataract surgery was not driven only by the high occurrence of such events.”

They emphasise that a CD4 cell count below 200 cells/mm$^3$ appeared to be associated with an especially increased risk of cataracts regardless of the use of HIV therapy, adding “no statistically significant excess risk was observed after initiation of abacavir, tenofovir, PIs [protease inhibitors], or NNRTIs [non-nucleoside reverse transcriptase inhibitors].”

The increased risk was apparent in all age ranges above 35 years of age.

The investigators are uncertain about the exact reasons why infection with HIV is associated with an increased risk of cataracts. Ocular disease was considered as a possible cause, as were the side-effects caused by anti-HIV drugs.

However, they add that the use of HIV therapy “could also be an indicator of a population at increased risk of developing illness rather than indicating the toxic effect on the eye induced by HAART [highly active antiretroviral therapy].”

Mindful that HIV has been associated with an increased risk of cardiovascular disease and other diseases of aging, the investigators conclude, “accelerated aging in the HIV-infected population cannot be excluded as a possible part of the explanation.”

Reference

Swiss show that concerns about potency of HIV therapy in context of non-subtype B infections are unfounded
Michael Carter
Published: 25 October 2011
Patients infected with non-B HIV subtypes have virological outcomes which are at least as good – if not better – than those seen in patients with subtype B infection, Swiss investigators report in the online edition of Clinical Infectious Diseases.

Some research has suggested that patients with non-B subtypes fare less well on HIV therapy. However, there was concern that such studies did not take into account host factors, such as race and cultural issues. It is therefore important that white Swiss patients infected with non-B HIV subtypes were eligible for inclusion in the Swiss study.

“In the past decade, a debate has arisen as to whether antiretroviral compounds are less active against non-B infections, because most antiretroviral drugs were designed to be used against subtype B infections,” write the authors. “Our findings indicate that these concerns are unwarranted.”

There are several distinct HIV subtypes as well as several recombinant forms of the virus. Subtype B predominates in Europe and North America and clinical trials leading to the approval of most antiretroviral drugs involved patients with subtype B.

Only 10% of global HIV infections are caused by subtype B. Studies performed in areas where non-subtype B infections predominate have yielded promising results about the effectiveness of antiretroviral therapy. However, these results cannot be generalised to western countries.

Therefore, investigators from the Swiss HIV Cohort Study examined the virological response to HIV therapy among white patients, comparing outcomes in individuals with subtype B and non-subtype B infections.

“HIV subtype and ethnicity are strongly correlated and ethnicity is potentially associated with treatment response and a different natural history of HIV,” comment the investigators. “This study allows the exclusion of potential bias due to different host genetic backgrounds.”

Data obtained between 1996 and early 2011 were included in the investigators’ analysis.
A total of 4729 patients (90%) had subtype B infection and 539 individuals (10%) were infected with non-subtype B virus. The most common non-B subtypes were AG (24%), A (23%), C (18%) and AE (13%). Baseline CD4 cell count and viral load were broadly comparable between the patients with subtype B and non-subtype B infections.

The incidence of virological failure (a rebound in viral load to above 1000 copies/ml after previous suppression below 400 copies/ml) was higher in patients with subtype B than among those with non-subtype B infections. Overall, the incidence was 4.3 failures per 100 person years for individuals with
subtype B infections compared to 1.8 failures per 100 person years for those with non-subtype B infections.

Patients with non-subtype B infections were similarly less likely to experience virological failure when analysis was restricted to treatment-naïve individuals who started therapy after 1999, with failure defined as rebound in viral load from below 50 copies/ml to above 500 copies/ml (1.4 per 100 person years vs. 2.6 per 100 person years).

An especially low risk of virological failure was associated with subtype CRF02_AG (HR = 0.54; 95% CI, 0.29-0.98) and subtype AG (HR = 0.39; 95% CI, 0.19-0.79).

The association between non-subtype B infections and a reduced risk of virological failure remained robust after controlling for age, sex, HIV transmission category, type of HIV therapy, as well as baseline CD4 cell count and viral load. This was the case for both definitions of virological failure (p = 0.009 and p = 0.041 respectively).

Reported adherence levels were similar for patients with subtype B and non-subtype B infections. Sensitivity analyses that took into account factors such as treatment interruption, mode of transmission, and baseline resistance did not have a significant impact on the investigators' findings.

“Previous concerns that antiretroviral treatment response might be hampered by development and testing of antiretroviral compounds in resource-rich countries with high subtype B prevalence are no longer tenable, and concerns that non-B infections are less susceptible to cART [combination antiretroviral therapy] are unwarranted,” conclude the investigators. “In fact, patients infected with particular non-B subtypes had lower virological failure rates than patients with subtype B infections in Switzerland.”

Reference

Reports: Uganda Brings Back Anti-Homosexuality Bill
Jim Burroway
October 25th, 2011
Bloomberg reports:
The legislation will be sent to the relevant session committee for consideration, Speaker Rebecca Kadaga told lawmakers today in a televised debate from the capital, Kampala.

Uganda’s parliament voted to reopen a debate on a bill that seeks to outlaw homosexuality that may be expanded to include the death penalty for gay people.

Giles Muhame, the former editor of the notorious Ugandan gay-baiting tabloid Rolling Stone (no relation to the U.S. publication by the same name) has more about the Parliamentary maneuvers and debates which, he says, brought the bill back. According to Muhame, the motion to revive the bill was made by MP Lt. Col. Sara Mpalwa, and was seconded by MP Crispus Ayena. A host of other contentious bills which were left unfinished when the Eighth Parliament expired last May were also reportedly brought back, along with all committee reports attached to the bills. Speaker Kadaga cited parliamentary procedures in Canada and India to justify the procedure of bringing bills back into Parliament without repeating the initial readings required to introduce a bill and refer it to committee.

The Speaker Kadaga was an early supporter for the Anti-Homosexuality Bill. She presided over Parliament in April 2009 in her role as Deputy Speaker when MP David Bahati sought approval to submit an Anti-Homosexuality Bill as a private member’s bill.

If these reports are correct, then the bill’s revival appears to be occurring despite assurances from representatives of President Yoweri Museveni’s cabinet that they have “thrown out” the bill. When that announcement was made last August, a Parliamentary spokesperson immediately shot back that the bill was “Parliament’s property.” Meanwhile, M.P. David Bahati, the bill’s sponsor, was elevated to the vice-chairmanship of the ruling party’s caucus in Parliament. In October, the caucus chairman was forced to step aside due to a corruption probe, and Bahati has since been elevated to acting caucus chair.

Since the inauguration of the Nineth Parliament, there had been rumors that that the Anti-Homosexuality Bill would be brought back sometime in the second half of August while others placed the timing in November. It was unclear what form the reintroduced bill would take. In early 2010, the Cabinet had recommended dismantling the bill and passing portions of it surreptitiously as amendments to other bills in the hopes of escaping worldwide attention. Many of those reported recommendations actually made their way into a Parliamentary report last May, barely a week before the Eight Parliament was scheduled to end. Media at that time carried several false reports that the death penalty provisions
had been dropped, but we now know that the death penalty, in fact, was still part of the bill. The Parliamentary Affairs Committee recommended that in the Clause 3 defining “aggravated homosexuality” and which specifies that “A person who commits the offence of aggravated homosexuality shall be liable on conviction to suffer death,” that the phrase “suffer death” should be replaced with “the penalty provided for aggravated defilement under Section 129 of the Penal Code Act.” Section 129 of the Penal Code Act mandates the death penalty for an unrelated offense of child molestation. Parliament ultimately failed to pass the bill due to a lack of a quorum because of controversy over another unrelated bill. If, as reported, this latest maneuver actually does revive the bill with its Parliamentary Affairs Committee report, then the bill’s passage might be imminent since the last step for its final passage last May was a final vote in Parliament.

**Boys Should Get Routine HPV Vaccination, CDC Panel Says**
*USA Today*, (10.25.2011) Liz Szabo

All children ages 11-12, boys as well as girls, should routinely be vaccinated against human papillomavirus, CDC’s Advisory Committee on Immunization Practices recommended Tuesday. CDC has recommended routine vaccination of girls for five years. Two years ago, ACIP issued a “permissive recommendation” on the shots for boys. Tuesday’s announcement upgrades this to “routine”—its highest recommendation.

Vaccinating boys will protect both them and their sexual partners from HPV-related cancer, doctors with CDC say. Although best known for causing cervical cancer, HPV also causes cancers of the anus, penis, back of the throat, vagina, and vulva, as well as genital warts. A study this week suggests HPV also is linked to heart disease in women.

“We are clearly seeing an epidemic of HPV-related head and neck cancers,” said Robert Haddad, chief of head and neck oncology at the Dana-Farber Cancer Institute in Boston.

Vaccinating boys is especially important given the low uptake of the shots among girls, just 44 percent received their first dose of the three-injection series, a recent CDC study found. Just 1.5 percent of boys have been vaccinated, said Anne Schuchat, director of CDC’s National Center for Immunization and Respiratory Diseases. Vaccinating boys will indirectly protect their future girlfriends or wives from cancer, Schuchat said.

“Today is another milestone in the nation’s battle against cancer,” said Schuchat. CDC, which typically adopts ACIP’s recommendations, is likely to formally approve adding HPV shots to the routine childhood immunization schedule within a couple of months, she said. Though many insurance plans already cover HPV shots for both boys and girls, a CDC recommendation will encourage others to pay for them as well, said Schuchat.

**Vitamin D Activates Immune Response to TB: Study**
*Agence France Presse*, (10.12.2011)

While researchers have long known that vitamin D is involved in the body’s response to TB, a new study shows it must be present at sufficient levels to trigger the immune response.

“Over the centuries, vitamin D has intrinsically been used to treat tuberculosis,” said lead author Mario Fabri. “Sanatoriums dedicated to tuberculosis patients were traditionally placed in sunny locations that seemed to help patients, but no one knew why this worked.”

“Our findings suggest that increasing vitamin D levels through supplementation may improve the immune response to infections such as tuberculosis,” said Fabri, who conducted the research while at the University of California-Los Angeles, and who now is at the Department of Dermatology at the University of Cologne, Germany.

Previously, the same research team showed that vitamin D plays an important role in the production of cathelicidin, a molecule that helps the innate immune system kill TB bacteria.

The new study shows that vitamin D is needed for the T-cells in the adaptive immune system to produce the protein interferon, which directs cells to attack the bacteria.

The finding could bolster TB treatment efforts in settings like Africa, as dark-skinned people are more likely to be deficient in vitamin D. This is because dark skin contains more melanin, which shields the body from ultraviolet rays and reduces vitamin D production.

“At a time when drug-resistant forms of tuberculosis are emerging, understanding how to enhance natural innate and acquired immunity through vitamin D may be very helpful,” said Barry Bloom, former dean of faculty at the Harvard School of Public Health and a study co-author.

**UNICEF Issues Statement Clarifying Reports Of Polio Cases In Madagascar**

UNICEF released a statement on Tuesday correcting an October 21 report by its office in Madagascar "expressing concern over a resurgence of polio in Madagascar after a routine health survey identified vaccine-derived poliovirus (VDPV) in several healthy children." According to the statement, "there was no re-emergence of polio in Madagascar," and "[t]he last wild poliovirus case in Madagascar was detected in 1997."

"A vaccine-derived poliovirus is a mutation of the virus that is present in the vaccine and in extremely rare instances can cause the disease it is meant to prevent," the statement says, adding, "In Madagascar, none of the children from whom the [VDPV] was isolated had paralysis" (10/25). "UNICEF officials said an investigation had been launched to see why the three children had the vaccine-derived poliovirus. They said low immunity on the island could be the reason," BBC News writes in a follow-up story to its previous report (10/25).

**Cholera Epidemic Hits Western, Central Africa**

"Western and central Africa are facing one of the biggest cholera epidemics in their history, the World Health Organization and the United Nations Children's Fund (UNICEF) said last month, in reporting that more than 85,000 cases of cholera have been registered since the beginning of the year, with nearly 2,500 deaths," according to Le Monde/Guardian. The newspaper writes, "UNICEF has identified three main cholera epidemic outbreaks in the Lake Chad basin, the West Congo basin and Lake Tanganyika," and "[f]ive countries—Cameroon, Ghana, Nigeria, the Democratic Republic of the Congo (DRC) and Chad—account for 90 percent of the reported cases and fatalities."

"The highest rates of contamination are in Chad, Cameroon—where nine out of 10 districts are affected—and western DRC, where the mortality rate is over five percent," UNICEF spokeswoman Marixie Mercado said, adding that the rate is over 22 percent in some regions," Le Monde/Guardian reports. "These figures are particularly dramatic, given that with appropriate treatment ... mortality can be brought down to one percent," the newspaper notes, adding that a lack of both medical care and public awareness are contributing to high mortality rates and continued spread of the disease (Vincent, 10/25).

**Council On Foreign Relations Releases Interactive Map Tracking Vaccine-Preventable Disease Outbreaks**

The Council on Foreign Relations' Global Health program "has released a user-friendly interactive map on the web that tracks 'Vaccine-Preventable Disease Outbreaks' around the world," Stewart Patrick, senior fellow and director of the council's Program on International Institutions and Global Governance, writes on the group's website. The council's Laurie Garrett and colleagues for the past three years "have been collecting and plotting global data on the incidence of several common infectious diseases that should be headed for extinction, given their vulnerability to inexpensive and effective vaccines," Patrick writes, adding, "The five most prevalent are measles, mumps, whooping cough, polio, and rubella. The entire database—to which experts and journalists are invited to contribute—is searchable by disease, region, and year" (10/25).

**Study Confirms Males and Females Have at Least One Thing in Common: Upregulating X**

ScienceDaily (Oct. 24, 2011) — In a study published in the journal Nature Genetics, a group of scientists including UNC biologist Jason Lieb, PhD, present experiments supporting a longstanding hypothesis that explains how males can survive with only one copy of the X chromosome. The finding provides clarity to a hotly debated topic in science and provides biologists with more information to interpret experiments involving genetic measurements in males and females.

"The issue is important because many diseases are tied to a defect in a regulatory mechanism within the cell," said Lieb, who is also a member of UNC Lineberger Comprehensive Cancer Center.

Women have two X chromosomes, while men have one X and one Y. The lack of a 'back up' copy of the X chromosome in males contributes to many disorders that have long been observed to occur more often in males, such as hemophilia, Duchenne muscular dystrophy, and certain types of color blindness. Having only one copy of X and two copies of every other chromosome also creates a more fundamental
problem—with any other chromosome, the gene number imbalance resulting from having only one copy would be lethal. How can males survive with only one X?

Biologists have been debating how organisms and cells manage the imbalance between X and other chromosomes for years, with the dominant theory being that both sexes up-regulate the expression of X-linked genes, essentially doubling their expression to "2X" in males and "4X" in females. Then, to correct the imbalance that now appears in females (since they have the equivalent of "4" Xs now and 2 of every other chromosome), females then 'turn off' one of the hyperactive X chromosomes, resulting in a balanced "2X" expression of those genes across both sexes.

The advent of new technology based on RNA sequencing and proteomic analysis has given scientists more accurate ways to measure gene expression, and some results published in the last few years have not supported the idea that X chromosomes up-regulate.

Lieb and his colleagues re-analyzed data used in previous analyses, along with new data from humans, mice, roundworms, and fruit flies and found more evidence that the up-regulation hypothesis is correct—but with some interesting twists across species. In mammals—humans and mice—both males and females up-regulate X chromosome gene expression and females then equalize expression by turning off the one X chromosome. In roundworms (C. elegans) the both female X chromosomes stay active, but the genes on both Xs are down-regulated by half to compensate in the females. In fruit flies (Drosophila melanogaster), males increase the expression of X chromosome genes, with no upregulation of X in females.

"There are several ways to get the same result and we are seeing how the dosage-balancing mechanism works in different species," says Lieb. "We also found that not all X-linked genes are dosage compensated to the same degree—adding another layer of complexity for scientists who study gene regulation."

**Journal Reference:**
Xinxian Deng, Joseph B Hiatt, Di Kim Nguyen, Sevinc Ercan, David Sturgill, LaDeana W Hillier, Felix Schlesinger, Carrie A Davis, Valerie J Reinke, Thomas R Gingeras, Jay Shendure, Robert H Waterston, Brian Oliver, Jason D Lieb, Christine M Disteche. Evidence for compensatory upregulation of expressed X-linked genes in mammals, Caenorhabditis elegans and Drosophila melanogaster. *Nature Genetics*, 2011; DOI: 10.1038/ng.948

**'Junk DNA' Defines Differences Between Humans and Chimps**

ScienceDaily (Oct. 25, 2011) — For years, scientists believed the vast phenotypic differences between humans and chimpanzees would be easily explained—the two species must have significantly different genetic makeups. However, when their genomes were later sequenced, researchers were surprised to learn that the DNA sequences of human and chimpanzee genes are nearly identical. What then is responsible for the many morphological and behavioral differences between the two species?

Researchers at the Georgia Institute of Technology have now determined that the insertion and deletion of large pieces of DNA near genes are highly variable between humans and chimpanzees and may account for major differences between the two species.

The research team lead by Georgia Tech Professor of Biology John McDonald has verified that while the DNA sequence of genes between humans and chimpanzees is nearly identical, there are large genomic "gaps" in areas adjacent to genes that can affect the extent to which genes are "turned on" and "turned off." The research shows that these genomic "gaps" between the two species are predominantly due to the insertion or deletion (INDEL) of viral-like sequences called retrotransposons that are known to comprise about half of the genomes of both species. The findings are reported in the most recent issue of the online, open-access journal *Mobile DNA*.

"These genetic gaps have primarily been caused by the activity of retroviral-like transposable element sequences," said McDonald. "Transposable elements were once considered 'junk DNA' with little or no function. Now it appears that they may be one of the major reasons why we are so different from chimpanzees."

McDonald’s research team, composed of graduate students Nalini Polavarapu, Gaurav Arora and Vinay Mittal, examined the genomic gaps in both species and determined that they are significantly correlated with differences in gene expression reported previously by researchers at the Max Plank Institute for Evolutionary Anthropology in Germany.

"Our findings are generally consistent with the notion that the morphological and behavioral differences between humans and chimpanzees are predominately due to differences in the regulation of genes rather than to differences in the sequence of the genes themselves," said McDonald.
The current analysis of the genetic differences between humans and chimpanzees was motivated by the group’s previously published findings (2009) that the higher propensity for cancer in humans vs. chimpanzees may have been a by-product of selection for increased brain size in humans.

**Journal Reference:**

**New Test Can Precisely Pinpoint Food Pathogens**

ScienceDaily (Oct. 25, 2011) — With Salmonella-tainted ground turkey sickening more than 100 people and Listeria-contaminated cantaloupes killing 15 this year, the ability to detect outbreaks of food-borne illness and determine their sources has become a top public health priority.

A new approach, reported online Oct. 14 in the journal *Applied and Environmental Microbiology* by a collaborative team led by Cornell scientists, will enable government agencies and food companies to pinpoint the exact nature and origin of food-borne bacteria with unprecedented accuracy, says food science professor Martin Wiedmann.

The standard method of tracing food-borne illness involves breaking up the DNA of bacteria samples into smaller pieces and analyzing their banding patterns.

But scientists often find that different strains of bacteria have common DNA fingerprints that are too genetically similar to be able to differentiate between them, making it difficult to establish whether the Salmonella that made one person sick was the same Salmonella that infected another person. This was the case in a Salmonella outbreak linked to salami made with contaminated black and red pepper that included 272 cases in 44 states between July 2009 and April 2010.

To surmount this challenge, Wiedmann adopted a genomic approach.

By sequencing the genome of 47 samples of the bacteria—20 that had been collected from human sources during the outbreak, and 27 control samples collected from human, food, animal and environmental sources before the outbreak—he and his team were able to rapidly discriminate between outbreak-related cases and non-outbreak related cases, isolating four samples believed to be connected to the pepper contamination.

In the process of doing so, he also found other links.

A Salmonella strain that led to a nationwide recall of pistachio nuts in 2009 turned up in samples from four people—only one of whom had reported eating pistachios.

Other connected cases suggested smaller outbreaks of which officials had been previously unaware.

"The use of genome sequencing methods to investigate outbreaks of food-borne bacterial diseases is relatively new, and holds great promise as it can help to identify the temporal, geographical and evolutionary origin of an outbreak," Wiedmann said. "In particular, full genome sequence data may help to identify small outbreaks that may not be easily detected with lower resolution subtyping approaches."

Wiedmann, research associate Henk den Bakker and other lab members developed the single nucleotide polymorphism (SNP) test that is specific to the 2009 pepper-associated outbreak with the help of researchers at Life Technologies Corp. They also collaborated with researchers at Washington State University and departments of health in New York City and New York state.

A similar approach has previously been used in hospital settings to trace pathogenic bacteria such as methicillin-resistant *Staphylococcus aureus*, but this is its first application for food-borne illness.

Wiedmann said he is continuing to perfect the method and use it to test other types of bacteria. The U.S. Food and Drug Administration and other agencies are also starting to use similar approaches.

**Journal Reference:**

**Fukushima Radiation Worse Than Feared**

A new analysis suggests that more radioactive contaminants were released from the crippled nuclear power plant than accounted for in official Japanese estimates.

By Bob Grant | October 26, 2011

Japanese officials underestimated the amount of radiation released from the Fukushima Daiichi power plant after March’s devastating earthquake and tsunami, according to a recently-published report analyzing data from a global array of sensors and detectors. In June, the Japanese government released a
report stating that $1.5 \times 10^{16}$ bequerels (Bq) of caesium-137—a harmful radioisotope that was released in large amounts from the Chernobyl disaster in 1986—and $1.1 \times 10^{19}$Bq of xenon-133, which does not pose a serious health risk as it’s not absorbed by the body or the environment, had spewed from the crippled power plant. But the new report, submitted and available for open peer review in *Atmospheric Chemistry and Physics*, revises those totals to almost twice the official estimate, calculating a release of $3.5 \times 10^{16}$ Bq caesium-137 and $1.7 \times 10^{19}$Bq of xenon-133.

The new findings are based on reading from dozens of sensors positioned within Japan and around the globe. Andreas Stohl, an atmospheric scientist with the Norwegian Institute for Air Research in Kjeller and first author on the paper, told *Nature* that the larger data set his team used to generate their estimates is likely the reason that they’re higher than the official Japanese numbers. For example, the Japanese government’s calculations did not take into account clouds of radioactive particles that blew out over the Pacific Ocean in the aftermath of the accident.

For detailed coverage of the nuclear disaster and its effects on people, wildlife, and the environment, see our *Fallout at Fukushima* series.

**Wide variations between US states in HIV mortality rates**

Michael Carter  
Published: 27 October 2011  

There are large differences in HIV-related mortality rates between individual US states, according to research published in the online edition of *AIDS*. Overall, the highest mortality rates were seen in southern states and were up to twice as high as the rates recorded in states with the lowest mortality.

“Effective interventions are needed to address these interstate disparities as part of a comprehensive approach to controlling the HIV epidemic,” write the investigators.

The introduction of effective antiretroviral therapy in the US in the late 1990s led to a significant fall in the number of deaths in patients with HIV. However, the overall risk of death remains higher for HIV-positive patients compared to individuals in the general population.

Moreover, there is little information on differences in HIV-related outcomes between US states. National statistics on HIV-related mortality show wide differences in mortality rates between states (from 0.8 to 8.3 per 100,000). However, these reports are potentially flawed because both HIV-positive and HIV-negative individuals are included in the denominator to determine HIV-related mortality in the population overall.

A more accurate way of determining mortality rates is to calculate case-fatality rates. This only assesses mortality in the HIV-positive population.

Therefore investigators conducted a study to determine case-fatality rates in 37 US states between 2001 and 2007. All these states used names-based HIV reporting. After controlling for age, sex, race/ethnicity and late diagnosis, the investigators compared case-fatality rates between individual states.

Overall, the **HIV case-fatality rate was 21 per 1000 HIV-infected person years**. The corresponding conventional HIV mortality rate was 6 per 100,000 person years.

Using the case-fatality rate substantially affected the position of some states in mortality ‘league tables.’ For instance, Wyoming moved up 27 places (from 36 to nine) and Iowa 17 places (from 34 to 17). In contrast, some states with a large HIV prevalence moved down, in the case of New York by 27 places (from three to 30).

“New York’s conventional HIV death rate was the third highest among states examined attributable in part to its high HIV prevalence,” note the authors. “Its comparatively low case-fatality rate...suggests good secondary and tertiary prevention of HIV disease, which could in part be due to earlier screening or entry into care, better adherence to medical instructions, or better care, compared to many other states.

**Colorado had the lowest adjusted case-fatality mortality.** Twelve of the fourteen states in the South had case-fatality which was twice as high (for example Georgia, RR = 2.53; 95% CI, 2.27-2.80).

“We identified significant interstate differences in US HIV case-fatality rates, with rates in many southern states being more than twice those in other states even after adjusting for differences in racial/ethnic and age distributions,” comment the investigators.

**Case-fatality rates were significantly higher in black patients compared to white patients (p < 0.001).**

The investigators calculated that the disparities between states meant that there were approximately 800 avoidable HIV-related deaths each year.
“Monitoring state-specific HIV case fatality rates could contribute to improved allocation of national and state resources for HIV-related care by focusing attention on states where better secondary and tertiary prevention of HIV is needed, such as those in the southern US,” conclude the researchers.

**Reference**


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**EACS: Does Maraviroc Intensification Promote Better CD4 Cell Recovery?**

Published on Tuesday, 25 October 2011 00:00

Written by Liz Highleyman

Adding maraviroc (Selzentry or Celsentri) to a suppressive antiretroviral regimen may help promote CD4 T-cell recovery in a subset of patients who experience poor immunological response to treatment, according to 2 studies presented at the 13th European AIDS Conference (EACS 2011) this month in Belgrade.

Some individuals taking antiretroviral therapy (ART) experience smaller-than-expected CD4 cell gains despite maintaining undetectable HIV viral load. The reason for poor CD4 cell recovery is not well understood, nor is there definitive therapy to raise CD4 counts.

**French Study**

In the first report, Lise Cuzin and fellow investigators with the French ANRS 145 Marimuno study team conducted a pilot study of maraviroc intensification in patients with insufficient immune restoration on ART.

The study included 57 participants with CD4 counts below 350 cells/mm³ and gains of less than 50 cells/mm³ per year, despite being on ART with a stable undetectable viral load (< 50 copies/mL) for at least 2 years.

**Almost all were men and the median age was 51 years.** They had been infected with HIV for a median of about 12 years and on combination ART for 10 years. The median current CD4 count was 238 cells/mm³, but the median nadir (lowest-ever level) of 61 cells/mm³ reflected a history of severe immune deficiency. Approximately half had exclusively CCR5-tropic HIV while the rest had dual/mixed tropism virus (able to use both CCR5 and CXCR4 coreceptors).

All patients added maraviroc to their stable regimen for 24 weeks, with doses adjusted to compensate for expected drug-drug interactions. Each patient acted as his or her own control.

**Results**

- Overall, in the full study population of 57 patients, the CD4 cell slope, or rate of increase, did not change significantly during maraviroc intensification.
- The slope was 15.8 cells/mm³ before intensification compared with 27.3 cells/mm³, a nonsignificant difference of 22.6 cells/mm³ (P = 0.08).
- However, the slope did increase significantly when looking at an on-treatment subgroup of 48 people who remained on therapy.
- In this group the slope was 19.4 cells/mm³ before intensification compared with 30.2 cells/mm³; the difference was again 22.6 cells/mm³, but it reached statistical significance in this analysis (P = 0.04).
- **No baseline characteristics predicted which patients would benefit from adding maraviroc, including viral tropism, using a protease inhibitor vs NNRTI regimen, or CD4 nadir.**
- **CD8 cell activation decreased significantly during intensification, then rose after maraviroc was discontinued.**
- There was no significant change in viral load during intensification; no one experienced virological failure, though 6 did have viral blips.
- Maraviroc intensification was generally well-tolerated, with only 1 severe adverse event possibly related to the addition of the new drug (mycobacterial adenitis).

Based on these findings, the researchers concluded, "In this study, intensification of stable HAART with a 24 weeks course of maraviroc was able to enhance CD4 cells recovery in a subgroup of patients with insufficient immune restoration despite long term non-detectable viral load."
**Italian Study**

Stefano Rusconi and colleagues with the HSL/MVC01/2008 study group conducted a maraviroc intensification study looking at 96 patients at 21 centers in Italy who experienced rapid HIV RNA suppression (< 50 copies/mL) on ART but poor immune reconstitution. Again most were men, with a median age of about 48 years.

This study was randomized, with half of participants adding maraviroc and the other half staying on their stable baseline suppressive ART regimen. By chance, the median baseline CD4 count was slightly higher in the maraviroc arm than in the stable ART arm (190 vs 170 cells/mm³). Follow-up continued for 48 months.

**Results**

- In an intent-to-treat analysis at week 48, significantly more participants in the maraviroc intensification arm than in the stable ART arm saw their CD4 cell count rise above 200 cells/mm³ (62.2% vs 35.6%; P = 0.01).
- The difference was no longer significant after adjusting for the higher baseline CD4 count in the maraviroc arm.
- The difference was also no longer significant when looking at a combined endpoint of CD4 count > 200 cells/mm³ plus at least a 25% increase from baseline (37.8% vs 24.4%; P = 0.17).
- In an on-treatment analysis of 77 patients, significantly more people in the maraviroc arm achieved a CD4 count > 200 cells/mm³ (63.2% vs 30.0%; P = 0.003).
- The difference remained significant for the combined endpoint (36.8% vs 17.5%; P = 0.05).
- After adjusting for baseline viral load, the difference in the single endpoint remained statistically significant, but the change in the combined endpoint was not.
- **Memory CD8 cells increased more in the maraviroc arm** compared with the stable ART arm.
- T-cell activation markers were reduced more in the maraviroc arm.
- Again, viral load did not change significantly, though there were 5 blips.
- Maraviroc was generally well-tolerated, with 3 possible related adverse events.

The researchers concluded that maraviroc was not superior to stable ART overall, but did appear to show a benefit for the simple CD4 count > 200 cells/mm³ endpoint, and for some patients.

They noted that maraviroc reduced activation and proliferation of T-cells, which might indicate that it has an effect on pro-inflammatory status. They added that the transitory reduction of activated CD4 cells accompanied by a rise in plasma IL-7 levels suggests a possible role of maraviroc in sustaining peripheral T-cell homeostasis.

Following the presentation, Peter Hunt from the University of California at San Francisco pointed out that a prior maraviroc intensification study by his group showed increased CD8 activation, while both of the later studies showed a decrease, indicating that further research is needed in this area. 10/25/11

**References**

L Cuzin, S Trabelsi, G Mouillot L et al. ANRS 145 Marimuno Study: a Multi-centre Prospective Pilot Study Evaluating Intensification of Stable Antiviral Therapy with Maraviroc in HIV-1-infected Patients with Insufficient Immune Restoration Despite Persistently Controlled Viral Replication. 13th European

**Bristol-Myers, Gilead Work on New Combo HIV Pill**


Bristol-Myers Squibb Co. and Gilead Sciences Inc. announced Wednesday a deal to develop and sell a once-a-day HIV pill that combines a popular protease inhibitor (PI) with a boosting agent.

Under the plan, Bristol-Myers will formulate, manufacture, and sell the combination treatment. The pill includes Bristol-Myers' PI Reyataz and Gilead’s cobicistat, which works to raise HIV drug levels in the blood by blocking an enzyme that breaks down drugs. Gilead is currently conducting mid- and late-stage human trials of the combination pill in newly diagnosed patients.

The two companies already work together on the three-drug pill Atripla, the first approved once-a-day HIV drug; it is now prescribed to more than half of new HIV patients. Atripla includes Sustiva, made by Bristol-Myers, and Gilead’s Viread and Emtriva.

Combination pills have become the foundation of HIV treatment, as they make regimen adherence much less difficult.
Gel Cuts Risk of Herpes Among Women, a Study Finds


An antiretroviral-based vaginal microbicide gel created to prevent HIV infections is even more effective against herpes, and a new study suggests why this is so.

In an earlier trial in South Africa, a tenofovir-based microbicide gel reduced heterosexually transmitted HIV among women using the product by 39 percent. In an unexpected twist, the gel also reduced herpes simplex virus-2 (HSV-2) infections by 51 percent.

“We were very pleasantly surprised to see such a potent effect,” said Dr. Salim Abdool Karim, a professor at the University of KwaZulu-Natal and Columbia University and one of the trial’s leaders.

The tenofovir-based vaginal gel cuts HSV-2 infections by disrupting an enzyme the virus needs to make copies of itself, according to the new laboratory study, which was conducted by researchers from the National Institutes of Health, Gilead Sciences Inc. and universities in Belgium and Italy.

In cultures of tonsil and cervical tissue, the gel cut herpes viral levels by as much as 99 percent. It also prolonged the lives of mice that were given HSV-2 skin infections.

Tenofovir taken as a pill inhibited HIV but not herpes: Direct application to the vaginal wall is apparently needed for the drug to work against herpes. Compared with the pill, tissue concentrations of the drug were up to 100 times higher with the direct application of the gel, said study co-author Leonid Margolis, chief of intercellular interactions at the National Institute of Child Health and Human Development.

The World Health Organization estimates that 20 percent of sexually active adults have genital herpes. In the United States, CDC estimates that 21 percent of sexually active women have it.

“I’m confident American women would accept” using such a gel, said Dr. Anna Wald, a herpes specialist at the University of Washington’s school of public health.

The complete study, “Topical Tenofovir, a Microbicide Effective Against HIV, Inhibits Herpes Simplex Virus-2 Replication,” was published in Cell Host & Microbe (2011;10(4):379-389).

Seasonal Rains, Flooding Lead To Cholera Outbreak In Nigeria

"Seasonal rains cause massive damage and disease throughout Nigeria each year, and this year’s onslaught comes as international experts warn West Africa is suffering from its worst cholera outbreaks in years,” the Associated Press/ABC News reports. According to UNICEF, Nigeria "had recorded more than 21,000 cholera cases this year by the end of September" and “[a]t least 694 people have died from the disease,” the news agency writes. Twenty-five of Nigeria’s 36 states have reported cholera cases, with most coinciding with local flooding, the AP notes, adding that "almost half of Nigeria’s 150 million people lack access to clean water and proper sanitation, according to the World Health Organization" (Gambrell, 10/26).

Reasons For Caution About Experimental Malaria Vaccine

Writing in KPLU’s "Humanosphere" blog, Tom Paulson responds to last week’s announcement of results from an ongoing clinical trial of an experimental malaria vaccine, saying, "Despite the hype and fanfare, many experts at the Seattle meeting said this experimental vaccine (known as RTS,S) actually so far represents only incremental progress—a scientific achievement which may still turn out to have little practical utility in the real world." Paulson says "the findings largely repeat earlier ‘interim’ results"; the cost of the vaccine, which has not yet been confirmed; and difficulty developing a malaria vaccine that offers an acceptable level of protection are reasons why the vaccine may not be successful (10/25).
Building better HIV antibodies
Caltech biologists create neutralizing antibody that shows increased potency

PASADENA, Calif.—Using highly potent antibodies isolated from HIV-positive people, researchers have recently begun to identify ways to broadly neutralize the many possible subtypes of HIV. Now, a team led by biologists at the California Institute of Technology (Caltech) has built upon one of these naturally occurring antibodies to create a stronger version they believe is a better candidate for clinical applications.

Current advances in isolating antibodies from HIV-infected individuals have allowed for the discovery of a large number of new, broadly neutralizing anti-HIV antibodies directed against the host receptor (CD4) binding site—a functional site on the surface of the virus that allows for cell entry and infection. Using a technique known as structure-based rational design, the team modified one already-known and particularly potent antibody—NIH45-46—so that it can target the binding site in a different and more powerful way. A study outlining their process was published in the October 27 issue of Science Express.

"NIH45-46 was already one of the most broad and potent of the known anti-HIV antibodies," says Pamela Bjorkman, Max Delbrück Professor of Biology at Caltech and senior author on the study. "Our new antibody is now arguably the best of the currently available, broadly neutralizing anti-HIV antibodies."

By conducting structural studies, the researchers were able to identify how NIH45-46 interacted with gp120—a protein on the surface of the virus that’s required for the successful entry of HIV into cells—to neutralize the virus. Using this information, they were able to create a new antibody (dubbed NIH45-46G54W) that is better able to grab onto and interfere with gp120. This improves the antibody's breadth—or extent to which it effectively targets many subtypes of HIV—and potency by an order of magnitude, according to Ron Diskin, a postdoctoral scholar in Bjorkman's lab at Caltech and the paper's lead author.

"Not only did we design an improved version of NIH45-46, our structural data are calling into question previous assumptions about how to make a vaccine in order to elicit such antibodies," says Diskin. "We hope that these observations will help to guide and improve future immunogen design."

By improving the efficacy of antibodies that can neutralize HIV, the researchers point to the possibility of clinical testing for NIH45-46G54W and other antibodies as therapeutic agents. It’s also plausible that understanding effective neutralization by powerful antibodies may be useful in vaccine development.

"The results uncover the structural underpinnings of anti-HIV antibody breadth and potency, offer a new view of neutralization by CD4-binding site anti-HIV antibodies, and establish principles that may enable the creation of a new group of HIV therapeutics," says Bjorkman, who is also a Howard Hughes Medical Institute investigator.

Natural killer cells could be key to anthrax defense

GALVESTON, Texas—One of the things that makes inhalational anthrax so worrisome for biodefense experts is how quickly a relatively small number of inhaled anthrax spores can turn into a lethal infection. By the time an anthrax victim realizes he or she has something worse than the flu and seeks treatment, it’s often too late; even the most powerful antibiotics may be no help against the spreading bacteria and the potent toxins they generate.

Now, though, University of Texas Medical Branch at Galveston researchers have found new allies for the fight against anthrax. Known as natural killer cells, they’re a part of the immune system normally associated with eliminating tumor cells and cells infected by viruses. But natural killer cells also attack bacteria—including anthrax, according to the UTMB group.

"People become ill so suddenly from inhalational anthrax that there isn’t time for a T cell response, the more traditional cellular immune response," said UTMB assistant professor Janice Endsley, lead author of a paper now online in the journal Infection and Immunity. "NK cells can do a lot of the same things, and they can do them immediately."
In test-tube experiments, a collaborative team led by Endsley and Professor Johnny Peterson profiled the NK cell response to anthrax, documenting how NK cells successfully detected and killed cells that had been infected by anthrax, destroying the bacteria inside the cells along with them. Surprisingly, they found that NK cells were also able to detect and kill anthrax bacteria outside of human cells.

"Somehow these NK cells were able to recognize that there was something hostile there, and they actually caused the death of these bacteria," Endsley said.

In further experiments, the group compared the anthrax infection responses of normal mice and mice that were given a treatment to remove NK cells from the body. All the mice died with equal rapidity when given a large dose of anthrax spores, but the non-treated (NK cell-intact) mice had much lower levels of bacteria in their blood. "This is a significant finding," Endsley said. "Growth of bacteria in the bloodstream is an important part of the disease process."

The next step, according to Endsley, is to apply an existing NK cell-augmentation technique (many have already been developed for cancer research) to mice, in an attempt to see if the more numerous and active NK cells can protect them from anthrax. Even if the augmented NK cells don't provide enough protection by themselves, they could give a crucial boost in combination with antibiotic treatment.

"We may not be able to completely control something just by modulating the immune response," Endsley said. "But if we can complement antibiotic effects and improve the efficiency of antibiotics, that would be of value as well."

Natural Intestinal Flora Involved in the Emergence of Multiple Sclerosis, Study Finds

Autoaggressive B-cells (green) in a lymph node close to the brain. The activation of the B-cells takes place in the germinal centres (blue) of the lymph node. The activated cells produce antibodies against the myelin layer in the brain, thus contributing to the occurrence of inflammatory reactions. (Credit: © MPI f. Neurobiology)
Multiple sclerosis is caused by a combination of genetic and environmental factors. For a long time, pathogens were believed to be such external influences. According to scientists from the Max Planck Institute of Neurobiology in Martinsried, however, it is apparently **not harmful bacteria that trigger multiple sclerosis, but beneficial ones**—specifically, the natural intestinal flora, which every human being needs for digestion. The researchers discovered that **genetically modified mice develop an inflammation in the brain similar to the human disease if they have normal bacterial intestinal flora. The microorganisms begin by activating the immune system's T cells and, in a further step, the B immune cells.**

The findings, published in the journal *Nature*, suggest that in humans with the corresponding genetic predisposition, the essentially beneficial intestinal flora could act as a trigger for the development of multiple sclerosis.

The human intestine is a paradise for microorganisms: it is home to roughly 100 billion bacteria made up from 2,000 different bacterial species. The microorganisms of the intestine are not only indispensable for digestion, but also for the intestine's development. Altogether, **this diverse community comprises between ten and one hundred times more genes than the entire human genome**. Scientists therefore frequently refer to it as the "extended self." However, the intestinal bacteria can also play a role in diseases in which the immune system attacks the body itself. **Intestinal bacteria can thus promote autoimmune disorders such as Crohn's disease and rheumatoid arthritis.**

On the one hand, the likelihood of developing multiple sclerosis, a disease in which proteins on the surface of the myelin layer in the brain activate the immune system, is influenced by genes. On the other, however, environmental factors have an even greater impact on the disease's development. Scientists have long suspected that it is caused by infectious agents. The Max Planck researchers now assume that multiple sclerosis is triggered by the natural intestinal flora.

This astonishing finding was made possible by newly developed genetically modified mice. In the absence of exposure to any external influences, inflammatory reactions arise in the brains of these animals which are similar to those associated with multiple sclerosis in humans—however, this only occurs when the mice have intact intestinal flora. **Mice without microorganisms in their intestines and held in a sterile environment remained healthy.** When the scientists "vaccinated" the animals raised in sterile conditions with normal intestinal microorganisms, they also became ill.

According to the Martinsried-based researchers, the intestinal flora influence immune systems in the digestive tract; **mice without intestinal flora have fewer T cells there.** Moreover, **these animals' spleen produces fewer inflammatory substances, like cytokines.** In addition, **their B cells produce few or no antibodies against myelin.** When the researchers restored the intestinal flora to the mice, their T cells and B cells increased their cytokine and antibody production.

"It appears that the immune system is activated in two stages: to begin, the T cells in the lymph vessels of the intestinal tract become active and proliferate. Together with the surface proteins of the myelin layer, these then stimulate the B cells to form pathogenic antibodies. Both processes trigger inflammatory reactions in the brain which progressively destroy the myelin layer—a process that is very similar to the way multiple sclerosis develops in humans," says Gurumoorthy Krishnamoorthy from the Max Planck Institute of Neurobiology. Thus, the disease is caused by changes in the immune system and not by disturbances in the functioning of the nervous system.

"Multiple sclerosis research has long been preoccupied with this question of cause and effect. Our findings would suggest that the immune system is the driving force here," says Hartmut Wekerle, Director at the Max Planck Institute in Martinsried.

The scientists are certain that the intestinal flora can also trigger an overreaction of the immune system against the myelin layer in persons with a genetic predisposition for multiple sclerosis. Therefore, nutrition may play a central role in the disease, as diet largely determines the bacteria that colonise the intestines. "Changing eating habits could explain, for example, why the incidence of multiple sclerosis has increased in Asian countries in recent years," explains Hartmut Wekerle.

Precisely which bacteria are involved in the emergence of multiple sclerosis remains unclear. Possible candidates are clostridiums, which can have direct contact with the intestinal wall. They are also a natural component of healthy intestinal flora but could possibly activate the T cells in persons with a genetic predisposition. The scientists would now like to analyse the entire microbial genome of patients with multiple sclerosis and thereby identify the differences in the intestinal flora of healthy people and multiple sclerosis patients.
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