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No Sex Education, Please, We're Arab

Inter Press Service, (11.22.2010) Cam McGrath

Lessons related to female and male anatomy, reproductive health, and STDs were recently cut from biology curricula for Egyptian students ages 12 to 17 on orders from Ministry of Education. Schools have been instructed not to teach about “reproduction and propagation” methods or “pollination and fertilization” genetics, and teachers have been told to disregard chapters on these subjects in existing textbooks.

New textbooks omitting the lessons are being printed, according to the weekly Al-Youm Al-Sabaa. Teacher-led discussions about the topics will “incorporate the latest information ... from sources other than school textbooks,” a ministry official said.

Sexual health lessons were first introduced after the 1994 International Conference on Population and Development, which asserted the right of youths to receive objective, scientific instruction about reproductive health. Egypt had been among just five Arab countries to include reproductive health in schools. Basic sex education is taught to secondary students in Tunisia, Morocco, Algeria, and Bahrain. Some private schools offer such lessons in Lebanon.

Surveys in Egypt show a low level of awareness about reproductive health and STD prevention, especially among women. Less than 2 percent of women in the poorest fifth of Egypt had a basic understanding of HIV, compared with only 16 percent for the top echelon. Men were better informed, but less than a third of the wealthiest males were aware that a person with HIV can appear healthy.

“In the 1960s and 1970s, when people discussed sexuality the focus was on good and bad relationships,” said sexual-health advocate Dr. Amal Abdel Hadi. “Now it is only about what is halal [permissible] or haram [sinful], which moves the whole issue into the religious realm.” “There will be
more misconceptions about sex, marital disharmony, and sexual harassment, and the prevalence of STDs will increase,” she predicted.

**Philadelphia’s Condom Contest**

*Philadelphia Inquirer*, (12.30.2010) Don Sapatkin

Through Jan. 14, entries continue to be accepted in Philadelphia’s contest to select a design for the wrapper of condoms distributed by the city. The design should be appealing, colorful, and “attractive to teens,” said Caroline Johnson, director of the city Department of Public Health’s Division of Disease Control.

The city has documented STD spikes among teens and young adults, and many of the same kids are getting infected again and again. HIV infections also have risen among youths and young adults. A boost in gonorrhea could presage more HIV infections, Johnson told a recent city Board of Health meeting.

Compared with the first nine months of 2009, city gonorrhea reports rose 33 percent the first nine months of 2010, preliminary data show. Chlamydia and infectious syphilis reports were both up 8 percent in the same period.

“So the prevention message is not getting through,” Johnson said. “We clearly are not changing behavior.” For casual and non-monogamous relationships, “using a condom should be the norm,” especially given rising STD numbers, she said.

“I think it’s time for a new awakening, a new approach,” Johnson said of the campaign, which will be supported by an $83,000 federal grant for STD prevention. Funding for the pilot campaign’s other promotional and associated efforts must come from the city’s shrinking budget, however.

Condom wrapper designs must be entirely original, and the contest is only open to city residents age 18 or older. In addition to having Philadelphia condoms carry their graphic, the winner will receive $250.

For more information, visit www.stdphilly.org.

**Dengue-Blocking Mosquitoes Field Trial To Kick Off Tuesday In Australia**

*Sydney Morning Herald* reports that a 12-week field trial involving the release of mosquitoes infected with a bacterium known to block the transmission of dengue will kick off Tuesday in several suburbs in north Queensland, Australia. "Laboratory research has shown that [the bacteria] Wolbachia acts like a vaccine for the mosquito, by monopolising resources needed by the dengue virus," according to the news service. "With up to 100 million people – largely from developing countries – being infected with dengue fever each year, a global solution was long overdue, [Scott O’Neill, of the University of Queensland, who is involved with the project] said" (Morgan, 1/3).

**Uganda To Vaccinate 2.5M People In Effort To Stop Yellow Fever Spread**

"Uganda is planning to inoculate 2.5 million residents in the East African nation's northern districts, where a yellow fever outbreak has killed 45 people and sickened another 183,” *CNN* reports (12/28). The *BBC* reports that though people living in Uganda first "began falling ill about a month ago in nine northern districts," a Ugandan health official “told the BBC the outbreak was confirmed as yellow fever on Christmas Eve” (12/27). Last week, the CDC "confirmed that the disease is yellow fever, the U.S. embassy in Kampala said in a statement," according to *CIDRAP News*. "Previous reports had suggested that the disease, which causes headache, fever, and vomiting of blood, was dysentery, Ebola fever, or, most recently, pneumonic plague” (Roos, 12/29). BBC notes: "The disease, transmitted by infected mosquitoes, was last recorded in Uganda almost 40 years ago, officials say" (12/27).

**Health Officials Concerned Over Possible 'AIDS Volcano' In Iran**

The *Financial Times* reports on health officials worries over a growing "AIDS volcano" in Iran, where "experts say rapid urbanisation and economic problems such as high inflation and unemployment have raised the marriage age and boosted divorce rates. These factors have led to increasing rates of drug addiction and sex outside marriage." The article notes HIV transmission via injecting drug users (IDUs) remains the main mechanism through which the virus is spread, but "sexual transmission is rising at an alarming rate, experts say." The Financial Times notes that health authorities in Iran "plan to implement a comprehensive five-year plan next year prioritising education of vulnerable women – including drug addicts, those married to drug users, and sex workers – and young people," to help slow the spread of the virus (Khalaj, 12/27).
**Clostridium bacteria infecting increasing numbers of hospitalized children**

Hospitalized children in the United States are more frequently becoming infected with the bacteria *Clostridium difficile*, according to a report posted online today that will appear in the May print issue of *Archives of Pediatrics & Adolescent Medicine*, one of the JAMA/Archives journals.

*C. difficile* can colonize the gastrointestinal tract and lead to infection, according to background information in the article. While some infected patients have no symptoms, others develop diarrhea, toxic megacolon (extreme inflammation and distention of the large intestine), perforated bowels or other potentially fatal complications. "In recent years, the incidence of *C. difficile* infection, the number of hospitalizations, associated deaths and severity in adults have been increasing," the authors write.

To evaluate the trends of *C. difficile* infection in children, Cade M. Nylund, M.D., of Uniformed Services University of the Health Sciences, Bethesda, Md., and colleagues analyzed records of hospitalized children in a national database of patients discharged from the hospital in 1997, 2000, 2003 and 2006. The database included about 10.5 million patients, of whom 21,274 (0.2 percent) had *C. difficile* infection.

The number of cases increased about 15 percent each year, from 3,565 in 1997 to 7,779 in 2006.

Children with *C. difficile* infection had an increased risk of death or colectomy (surgery to remove all of part of the colon), longer hospital stays and higher hospitalization charges.

Some children appeared more likely to become infected, including those who were white, lived in the West or in urban areas, had private insurance or had other co-occurring diseases, such as inflammatory bowel disease. The risk of infection was lower among black or Hispanic children, those who lived in the South, those admitted to rural hospitals, those with Medicaid/Medicare insurance and those who had self-pay or no-pay insurance status.

Unlike recent trends in adults, however, the authors did not observe an increase in severity over time among children infected with *C. difficile*.

The increased risk of *C. difficile* infection may be due to a widespread dissemination of a more virulent strain of the bacteria, the authors note. "There may also be increasing awareness among health care providers, leading to increased testing in symptomatic patients," they write.

"The population-based data in our study provide additional evidence that *C. difficile* infection cases have a significant effect on the pediatric population," the authors conclude. "Our study supports previous reports that *C. difficile* infection is increasing among hospitalized children and provides a background for understanding changing trends and risk factors of *C. difficile* infection in children. Increasing awareness of these risk factors and of an upward trend in hospitalized children with *C. difficile* infection is the first step in controlling this important infection."

NYTimes, January 3, 2011

**City’s Graphic Ad on the Dangers of H.I.V. Is Dividing Activists**

By Anemona Hartocollis

The advertisement opens like a French film noir, showing portraits of melancholy-looking men standing against a shadowy black-and-white backdrop of menacing New York City streets. “When you get H.I.V.,” the narrator intones, “it’s never just H.I.V.”

To music that telegraphs calamity, the advertisement warns of osteoporosis, “a disease that dissolves your bones,” flashes a gory picture of anal cancer and delivers a punch line about the importance of using condoms.

The New York City Health and Mental Hygiene Department released the advertisement on YouTube and television in early December, intending to show that even though an H.I.V. diagnosis is no longer a death sentence, neither do H.I.V. drugs guarantee good health. But since then, several mainstream gay groups have organized against it, calling it stigmatizing and sensationalistic, and demanding that the city pull it from circulation. And in response, other gay activists have rushed to the health department’s defense.

“IT’s about time,” Larry Kramer, the writer and a founder of Act Up, wrote in an e-mail to friends and fellow activists after seeing the spot. “This ad is honest and true and scary, all of which it should be. H.I.V. is scary, and all attempts to curtail it via lily-livered nicey-nicey ‘prevention’ tactics have failed.”

For New York, the H.I.V. advertisement is just the latest in a series of graphic YouTube public service ads tackling health issues like smoking, obesity and childhood poisoning, created to reach young people through a medium they understand.

The H.I.V. public service ad falls into a tradition of attention-grabbing messages going back to the high school driver’s education films of car crashes on rain-slicked highways, and the graphic films about
shown to Army recruits. A more recent model might be the “Truth” antismoking campaign, which tapped into young people’s suspicions of the adult world, sponsored by the American Legacy Foundation, as part of the 1998 tobacco settlement.

Health officials said the spot had also appeared on television and would continue to run through mid-January on TimeWarner, Cablevision and FiOS cable networks, WNYW (Channel 5) and WPIX (Channel 11).

Some gay organizations are not happy.

“We know from our longstanding H.I.V. prevention work that portraying gay and bisexual men as dispensing diseases is counterproductive,” said Marjorie Hill, chief executive of Gay Men’s Health Crisis. “Studies have shown that scare tactics are not effective.”

Jarrett Barrios, president of the Gay and Lesbian Alliance Against Defamation, known as Glaad, said the advertisement “misses the mark in fairly and accurately representing what it’s like to live with H.I.V./AIDS.”

But city health officials say the advertisement was tested on focus groups of the target audience — primarily Latino and black men between ages 18 and 30 — and also reflected the city’s experience of what worked in its past antismoking campaigns, which included stomach-turning images of amputated fingers, tracheotomies and what was depicted as a dead smoker’s aorta.

“One of the points they kept making is you need to hit hard and do something to counteract the pharmaceutical ads that say having H.I.V. is a walk in the park,” Dr. Monica Sweeney, assistant commissioner of the city’s bureau of H.I.V. prevention and control, said recently.

Dr. Sweeney said the city stood by the advertisement and was pleased that it was getting attention, even if through controversy.

The campaign, which cost $726,000, was produced by DCF Advertising and financed by a federal grant, officials said.

In the last few days, the National Association of People with AIDS and the H.I.V. Health and Human Services Planning Council of New York have added their voices to the opposition. Another group, Housing Works, also opposes the spot, a spokesman said.

In a Dec. 17 letter to Mayor Michael R. Bloomberg, the planning council, which includes service providers and people living with H.I.V./AIDS, said that while it was true that older adults with H.I.V. might be at greater risk of developing cancer, dementia and osteoporosis, the ad “implies that young adults living with H.I.V. suffer from these conditions, too — and that is false.”

The letter said that getting more advice from gay men into how to promote H.I.V. prevention, and “acknowledging their resilience in the face of this epidemic, will be far more successful than perpetuating outdated images of sickness, dying and death.”

The advertisement’s critics cited research by Peter Salovey, a psychology professor at Yale, and colleagues, who found that threatening messages did not necessarily lead people to adopting healthier behaviors and could be counterproductive. The researchers also found that many preventive health behaviors, like using sunscreen, could be better promoted through positive than negative messages. In a 2002 paper, Dr. Salovey and his colleagues said, “One could hypothesize that condom use, because it is a preventive behavior, would be better promoted by stressing its benefits.”

But Dr. Salovey said he had also published research showing that negative-consequence ads did work better for some health campaigns, including one in which low-income minority women were urged to undergo H.I.V. testing.

He added that he could not pass judgment on New York’s condom advertisement. “As our research shows,” he said in an e-mail, “there are situations when messages stressing benefits are more persuasive and other situations when messages stressing the risks of not taking action are more persuasive.”

Dr. Howard Grossman, a Manhattan internist and H.I.V. specialist, said the city’s approach was worth trying.

“Younger gay men are not making some kind of rational choice to have unprotected sex the way many activists are maintaining in this disagreement,” Dr. Grossman said. “These younger people are, like most young people having sex, living in the moment and making split-second, uninformed choices about unprotected sex.

“The point is that there’s a whole new generation out there who needs to learn that H.I.V. is a disease to stay away from, and so a fear-based ad directed at them is a whole new thing.”

Mr. Kramer, the author of “The Normal Heart,” an autobiographical play about AIDS in 1980s New York City, said H.I.V. treatment had bred complacency and a false sense of safety to gay men too young to remember a generation of gay men dying.
“Everybody thinks all you need to take is one pill, which is just malarkey,” said Mr. Kramer, who is H.I.V.-positive. “Nobody takes one pill. I mean, I take like 10.”

Uganda’s High Court Ruling Against “Hang Them” Tabloid Campaign
Jim Burroway
January 3rd, 2011
Ugandan High Court ruling barring Rolling Stone from publishing names and addresses of private LGBT citizens (Click to download: 1.3MB/10 pages)

As we reported earlier this morning, Uganda’s high court released a ruling permanently prohibiting the tabloid Rolling Stone (no relation to the venerable U.S. publication by the same name) from continuing its public vigilante campaign against that country’s LGBT community. We now have the text of that ruling (PDF: 1.3 MB/10 pages), which was signed on December 30 by Judge Musoke Kibuuka.

Judge Kibuuka found that the actions of Rolling Stone violated the privacy rights of LGBT Ugandans, and as well as the right to human dignity and protection from inhuman treatment. Of the latter, Judge Kibuuka wrote:

Upon that objective test, court would easily conclude that by publishing the identities of the applicants and exposing their homes coupled with the explicit call to hang them because “they are after our kids”, the respondents extracted the applicants from the other members of the community who are regarded as worthy, in equal measure, of human dignity and who ought to be treated as worthy of dignity and respect. Clearly the call to hang gays in dozens tends to tremendously threaten their right to human dignity. Death is the ultimate end of all that is known worldly to be good. If a person is only worthy of death, and arbitrarily, then that person’s human dignity is placed at the lowest ebb. It is threatened to be abused or infringed.

For the objective test, the court cited a Canadian case from 2002, when a man published an advertisement showing four scriptural passages next to an image of two stick men holding hands inside a circle with a line through it. The CBC notes that the decision was overturned by the Saskatchewan Court of Appeal in 2006. It’s unclear whether the grounds for that 2006 decision would have any bearing on the Ugandan case.

The court rejected Rolling Stones argument that because homosexuality is illegal in Uganda, the applicants were not eligible for protection because they were criminals:

It must be noted that this application is not about homosexuality per se. it is about fundamental rights and freedoms. However, court not agrees that section 145, of the Penal Code Act renders every person who is gay a criminal under that section of the Penal Code Act. The scope of section 145 is narrower than gayism generally. One has to commit an act prohibited under section 145 in order to be regarded a criminal.

"Hang Them; They Are After Our Kids", published in the October 2, 2010 edition of the Ugandan tabloid Rolling Stone (Names, places and photo obscured by BTB. Click to enlarge)

This point may serve as fodder for those who support the passage of the proposed Anti-Homosexuality Bill. That bill greatly expands the definition of what constitutes homosexual behavior far beyond the sex act. It will also criminalize advocacy on behalf of LGBT people and make criminals of family members who refuse to report their loved ones to police. If that bill were to become law, merely bringing this case to court and arguing in defense of LGBT people could be taken as “promotion” of homosexuality, leading to fines and a sentence of between five to seven years. The bill may be brought to a vote during a lame-duck session of Parliament following the February 18 elections.

The court issued a permanent injunction against Rolling Stone, “their servants and agents, from any further publications of the identities of the persons and homes of the applicants and homosexuals generally.” The order only applies to Rolling Stone, but human rights advocates believe that it may serve as a precedent for other tabloids to follow. Red Pepper and Onion (also no relation to the U.S. satirical newspaper by the same name) have also engaged in vigilante campaigns in recent months.

The judge awarded each applicant 1,500,000 Uganda Shillings (US$650) for damages, plus court costs.

Giles Muhume, Rolling Stone editor, remained defiant in the face of the court ruling. In a press release, he said that “homos had a short-lived smile today” but that Rolling Stone would appeal the decision. Calling the ruling a risk to media freedom, Muhume added, “The newspaper will fight homos on different fronts. Our supporters should remain strong – the agents of the devil shall be defeated.”
**Hepatitis Warning: Possible Virus Exposure at Two Christmas Masses**

*Newsday (Melville)*, (01.04.2011)  Delthia Ricks; Paul Larocco

Nassau County health officials are warning about potential hepatitis A virus exposure during Holy Communion at two Christmas Day Masses at Our Lady of Lourdes Church in Massapequa Park.

“An individual tested positive for hepatitis A who is involved in the Communion process,” said Mary Ellen Laurain, spokesperson for the county Department of Health. “We feel transmission [risk] is low,” she said, adding that only a few people were potentially exposed. “And to protect the public from potential illness, those who received Holy Communion on Dec. 25 should receive prophylactic treatment.” The church has 30 Eucharistic ministers who may assist priests at crowded Masses.

The health department is offering participants immune globulin or hepatitis A vaccine. A clinic will be held at the church, 855 Carmans Rd., 3-8 p.m. on Tuesday and from 9 a.m. to 3 p.m. Wednesday.

Hepatitis A has a “fecal/oral route of transmission,” said Dr. Melissa Palmer, medical director of New York University Hepatology Associates in Plainview. Outbreaks often are associated with food handled by a person with inadequate hand-washing habits. A Communion wafer is as likely as other ingested items to become contaminated, Palmer said.

“It was probably a full church” during the 10:30 a.m. and noon Masses, said Sean Dolan, a spokesperson for the Diocese of Rockville Centre. However, it is not known how many people attending received wafers during Holy Communion.

It is too early to speculate about any new hygiene practices as a response, Dolan said. The rectory voice mail referred questions to the health department. “We pray that no one comes down with this virus,” said a message on the diocese website.

For more information, congregants at risk of exposure can call the Department of Health at 516-227-9496.

**Study into HIV 'Cure' Seeks Volunteers**

*Bay Area Reporter (San Francisco)*, (12.23.2010)  Matt Baume

San Francisco researchers led by Dr. Jacob Lalezari are looking for HIV-positive volunteers to participate in a groundbreaking study that uses gene therapy to modify patients’ immune systems.

The study is based on work conducted in Germany on an HIV-positive man treated for leukemia. In 2007, the man received a bone marrow transplant from a donor with a rare genetic mutation that eliminates the CCR5 protein from the immune system. Without CCR5, HIV is unable to enter and infect T-cells. Three years after the transplant, HIV is undetectable in the patient.

Lalezari, medical director at Quest Clinical Research and assistant clinical professor of medicine at the University of California-San Francisco, and his team are exploring a less invasive approach. Rather than undergo a costly and painful bone marrow transplant, volunteers will have their blood filtered to extract immune cells. Those cells will then be treated with a zinc finger nuclease that will remove the gene that produces the CCR5 protein. Following cultivation for about three months, a large dose of treated immune cells will be re-infused in the originating patient in the hope they “take root” and replace vulnerable cells.

The treatment is expected to be painless and carry a relatively low risk of side effects. By contrast, the patient in the German study received chemotherapy and immunosuppressive drugs to prevent transplant rejection.

Interested volunteers must fit a very specific profile. Researchers are looking for HIV-positive people who have not taken antiviral drugs in the last 12 weeks, who are negative for hepatitis B and C, and whose T-cell counts are higher than 500. For more information, contact Quest at 415-353-0800 or e-mail Lalezari at drjay@questclinical.com.

**Uganda's Yellow Vaccine Campaign Postponed**

Uganda's health ministry has "postponed the mass vaccination exercise against yellow fever due to the scarcity of the vaccine," *New Vision* reports. "Vaccination is not starting today because we have not yet got any feedback regarding the availability of the vaccine," said Paul Kaggwa, the assistant commissioner of health at the ministry. The health ministry is looking into working with UNICEF and other international agencies in an effort to secure enough vaccines, Kaggwa said (Nninsima, 1/4). The vaccine scarcity "comes at a time when Cameroon is also battling yellow fever and the available 1.5 million doses have to be shared between the two countries," according to the *Daily Monitor*. 

Kenya Mugisha, who led the National Task Force on Yellow Fever to Northern Uganda, "said the situation is now under control with no new cases
registered in recent days while most of those who were admitted have been discharged from hospital. "The situation is calm, by Friday, only 23 people were still contained in hospitals," he said (Layero/Makumbi, 1/3/2011)

**When Men Fear Telling Their Wives About HIV**

*Inter Press Service*, (12.30.2010) Zofeen Ebrahim

Near Karachi, two men who work at an HIV/AIDS organization recently discussed how disease-related misinformation and stigma hamper HIV prevention.

"Not only did I share needles, [I] also visited brothels," says "Ahmad," the pseudonym of a peer-educator diagnosed HIV-positive two years ago, just three months into his marriage. "I had no clue how risky my entire behavior was." "My worst fear is that if I disclose my status, my wife will leave me," he said. "I can’t bear the thought of that."

Ahmad and his wife had agreed they did not want children, so they were already having protected sex. He continues to use that as an excuse and tries to work late most nights. Though he has not told her of his infection, Ahmad has taught her all he knows about the disease.

"Imran," Ahmad’s co-worker, was diagnosed with HIV eight months ago and has yet to tell his wife of five years. "When I take people with AIDS to the hospital, doctors will wear two and sometimes three pairs of gloves [and] stay as far away from them as possible," Imran said. "If doctors are so uncomfortable around us, what can you expect from those less knowledgeable?"

A 2008 report by UNAIDS and the UN Office on Drugs and Crime found a “hidden epidemic” of HIV in the wives of injection drug users (IDUs). Prevalence among these women ranged from 5 percent to 15 percent, depending on the area surveyed. Over 70 percent of the wives reported no condom use at last sex with their husbands.

Eventually, most HIV-positive IDUs do reveal their serostatus to their spouses, said Dr. Saleem Azam, who has worked with IDUs for 25 years. "But it takes time and counseling for them to brace themselves for the disclosure, given the strong societal pressures they encounter."

**Assessing the Impact of Mass Rape on the Incidence of HIV in Conflict-Affected Countries**

*AIDS Vol. 24; No. 18: P. 2841-2847*, (11.27.2010) Virginie Supervie; Yasmin Halima; Sally Blower

The study investigators sought to quantify the potential impact of mass rape on HIV incidence in seven conflict-affected countries in sub-Saharan Africa with severe AIDS epidemics using an uncertainty analysis of a risk equation model.

Using a mathematical model, the potential impact of mass rape on increasing HIV incidence in women and girls in Burundi, Democratic Republic of Congo (DRC), Rwanda, Sierra Leone, Somalia, southern Sudan, and Uganda was evaluated. The model was parameterized with data from UNAIDS, the World Health Organization and the US Census Bureau’s International Database. Incidence data from UNAIDS/WHO were used for calibration.

Mass rape could result in approximately five HIV infections per 100,000 females per year in the DRC, Sudan, Somalia, and Sierra Leone; double the number in Burundi and Rwanda; and quadruple the number in Uganda. The number of females infected annually due to mass rape is likely to be relatively low in Somalia (127, [median (interquartile range 55-254)]) and Sierra Leone (156, [median (IQR 69-305)]). In the DCR and Uganda, figures could be high: 1,120 [median (IQR 527-2,360)] and 2,172 [median (IQR 1,031-4,668)], respectively. In Burundi, Rwanda, and Sudan the numbers are likely intermediate. Under extreme conditions, 10,000 females in the DRC and 20,000 in Uganda could be infected per year. "Mass rape could increase annual incidence by approximately 7 percent [median (IQR 3-15)]," study results showed.

"Interventions and treatment targeted to rape survivors during armed conflicts could reduce HIV incidence," the investigators concluded. "Support should be provided both on the basis of human rights and public health."

**Parishioners Get Treatments**

*Newsday (Melville)*, (01.05.2011) Delthia Ricks

Health officials say a case of hepatitis A in a person affiliated with Our Lady of Lourdes Church has so far not resulted in any further infections. During the 10 a.m. and noon Christmas Day Masses, the ailing
person assisted in the distribution of Holy Communion wafers, which many of the estimated 1,300 persons in attendance consumed.

“There have been no secondary transmissions from the original person,” said Mary Ellen Laurain, spokesperson for the Nassau County Department of Health (DOH).

The patient became ill the day after Christmas, sought a doctor’s care, and was hospitalized. The subsequent hepatitis A illness was reported to Nassau County DOH as required by law, Laurain said.

Nassau County DOH offered preventive hepatitis A vaccinations or immune globulin treatment at a clinic held Tuesday at the Massapequa Park parish. More than 400 church members stopped by for the injections; DOH also is providing the shots at the parish on Wednesday. The efforts are a precaution, as the potential for widespread infection among parishioners is remote.

A spokesperson for the Diocese of Rockville Centre, Sean Dolan, said the church is emphasizing the importance of hand-washing among those serving Holy Communion but is not requiring the use of gloves. Proper hand-washing helps prevent transmission of hepatitis A, which spreads through fecal-oral contamination.

A Place for Second Chances: Tabor House Marks 20 Years of Helping Homeless Men with HIV/AIDS Live Their Lives and Regain Their Pride

Hartford Courant, (01.02.2011) Steven Goode

Hartford’s Tabor House is celebrating 20 years of providing refuge and support to homeless men with HIV/AIDS. Founded by the Sisters of St. Joseph, Tabor House has two locations—one on Brownell Avenue in the city’s Frog Hollow neighborhood and the other on Maple Avenue.

Sister Anne Kane, Tabor House’s director, said the organization’s early days were spent providing comfort and dignity to its residents. “In the beginning, they literally came to die,” she said. “We tried to provide an atmosphere of peace. Convalescent homes weren’t taking them in and their families were afraid. These people were shunned; they had no place to go.”

Thanks to advances in HIV/AIDS treatment, the focus has changed. Tabor House now helps maintain residents’ health by offering treatment, behavioral group therapy, substance abuse referrals, and case manager support. Residents are encouraged to return to school or learn a trade, but they set their own goals.

Tabor House’s aim is to have clients leave the house and successfully re-enter society. But this can take years to accomplish, and no one is sent away before they are ready. “Now a happy ending is they move out,” said Kane.

Chris Ryan said his goal when he was accepted into Tabor House was to get counseling, save money, and restore his health. He accomplished that in two years and has been living on his own for three years. He works for a Hartford-area property management company and remains drug-free. “Once you get healthy, you have to go to the next step,” he said. “They can only do so much for you.”

Study confirms 2 vaccine doses protect children from chickenpox

[EMBARGOED FOR JAN. 5, 2011] Two doses of the varicella, or chickenpox, vaccine provide excellent protection in children against this highly contagious and, in some cases, severe disease. To be published in the February 1 issue of The Journal of Infectious Diseases, the findings support the two-dose vaccine regimen recommended in the United States since 2006. (Please see below for a link to the study online.)

The Centers for Disease Control and Prevention (CDC) began recommending a single dose of varicella vaccine in children aged 1 to 13 years old in 1995. Although the incidence of varicella fell by 90 percent after introduction of the vaccine, there was a high rate of breakthrough varicella illness in immunized children and continuing outbreaks of varicella among children despite high rates of vaccination. Studies also showed that the single-dose vaccine’s effectiveness was less than 90 percent. Given the evidence, CDC in 2006 began recommending a second dose of the vaccine for children 4 to 6 years old.

Although data suggest that two doses of varicella vaccine are associated with higher levels of antibody than is one dose, this study is the first to assess the clinical effectiveness of two doses of the vaccine in the general population. Eugene D. Shapiro, MD, and colleagues at Yale University and collaborators at Columbia University conducted active surveillance in an area in Connecticut and discovered 71 cases of varicella in children aged 4 or older. None of the children had received two doses of vaccine, 66 (93 percent) had received one dose, and 5 (7 percent) had received no vaccine.

The investigators then compared the effectiveness of two doses of vaccine versus one dose in a case-control study, using 140 matched controls. The effectiveness of one dose in preventing varicella was 86.0
percent, while the effectiveness of two doses was 98.3 percent. According to Dr. Shapiro, "The odds of developing varicella were 95 percent lower in children who had received two doses of the vaccine compared with those who had received only one."

The results of this study suggest that countries immunizing children with only one dose of varicella vaccine should consider changing to a two-dose regimen. But, the authors emphasized, "There should be continued monitoring of the effectiveness of two doses to assure that its high degree of effectiveness is sustained."

In an accompanying editorial, David W. Kimberlin, MD, of the University of Alabama at Birmingham, agreed with the study authors, noting that this study is the first to evaluate the effectiveness of two doses of varicella vaccine in a "real-world" setting. "The high effectiveness of 98.3 percent found in this investigation supports the programmatic change instituted four years ago," Dr. Kimberlin noted.

**Fast Facts:**
1) In this study, the odds of developing varicella (chickenpox) were 95 percent lower in children > 4 years of age who had received two doses of the varicella vaccine compared with those who had received only one dose.
2) Of the 71 cases of varicella noted in the study, none of the subjects had received two doses of vaccine.
3) The effectiveness of two doses of vaccine in protecting against varicella in the study population was 98.3 percent.

**Where MRSA colonizes on the human body**

**Rhode Island Hospital study identifies quantity and locations of MRSA colonization**

PROVIDENCE, RI – When methicillin-resistant *S. aureus* (MRSA) is carried in the nose (nares), it is a risk factor for an invasive infection, including a surgical site infection. Some studies have found that the heavier the carriage of MRSA in the nose, the greater the risk of transmission to others and the greater risk of infection to the patient. Few studies to date have assessed the differences in quantity of MRSA at different body sites. A new study from Rhode Island Hospital now sheds light on both the quantity of MRSA at different body sites and the relationship between the quantities at different sites. The study is published in the *Journal of Clinical Microbiology*.

The investigators found that culturing the nose was more likely to reveal MRSA than culturing under the arms (axilla), the groin, or perineum (skin between the rectum and genitals). The researchers also found a strong correlation between the quantity of MRSA in the nose and the likelihood that other body sites were colonized with MRSA—when there was a large quantity of MRSA in the nose of a patient, it was likely that there was also a large quantity of MRSA in their axilla, perineum, or groin as well.

Leonard Mermel, DO, medical director of the department of epidemiology and infection control at Rhode Island Hospital and lead author says, "This study shows us that the quantities of MRSA at different body sites are highly correlated. Also, if screening cultures are to be done for MRSA, it is best to screen the nose and groin to get the highest yield."

Mermel concludes, "We hope that future studies will assess whether or not a greater number of body sites colonized with MRSA or a greater quantity of MRSA at those body sites impacts the likelihood of future MRSA infections."

The researchers were unable to find a correlation between the number of body sites with MRSA and likelihood of having an active MRSA infection at the time the cultures were obtained or in the year before the study. Of the patients who had MRSA in their nose at the time the cultures were obtained, the quantity of MRSA was surprisingly lower in those patients who had an active MRSA infection as opposed to those that did not have an active infection at that time, or during the year prior to enrollment.

**UK Gay Men’s Sex Survey: new data on age, strategic positioning, condom failure and HIV testing**

Roger Pebody
Published: 06 January 2011

Sexual behaviours that are most likely to result in acquiring HIV are most common in teenagers, while those behaviours most likely to pass on HIV are most common among men in their thirties. These are some of the results of the 2008 United Kingdom Gay Men’s Sex Survey, released last month.

The survey also suggests that more men than ever have tested for HIV (including one in ten at a GP's surgery) but that less than half had done so in the previous year. There is also some evidence of 'strategic
positioning’ during oral sex and information about behaviours which lead to condoms splitting or coming off.

At the same time, researchers have issued preliminary data from a similar survey conducted across Europe in 2010. With over 180,000 men completing the questionnaire, it is the largest sexual health survey ever conducted with gay and bisexual men.

**UK Gay Men’s Sex Survey**
The Gay Men’s Sex Survey uses a self-completion questionnaire that is available in a booklet form (distributed by health promotion organisations) and in an online version (promoted by a number of commercial gay, health promotion and gay community websites). For the 2008 edition 7,461 valid responses were received from gay or bisexual men living in the UK.

**Age**
The researchers analysed how engaging in specific sexual risk behaviours varied by age. They identified certain behaviours which might result in a participant acquiring HIV, and other behaviours which might result in him passing on HIV.

Looking first at behaviours which could lead to HIV acquisition, this analysis is limited to men who reported that they had tested HIV-negative or who had never tested at all.

- Taking ejaculate in the mouth during oral sex with a partner of unknown or HIV-positive status. 40% of men under the age of 20 reported this—higher than any other age group.
- Receptive unprotected anal intercourse with a partner of unknown or HIV-positive status. 23% of men under the age of 20 reported this—again higher than any other age group.
- Using poppers during receptive unprotected anal intercourse with a partner of unknown or HIV-positive status. 5% of under-20s reported this, but the numbers did not vary by age group.

Now turning to behaviours which could lead to HIV transmission, this analysis is limited to men who were diagnosed HIV positive or who had never tested at all.

- Ejaculating in the mouth of a partner of unknown or HIV-negative status. 46% of men in their thirties reported this—higher than any other age group.
- Insertive unprotected anal intercourse with a partner of unknown or HIV-negative status. 28% of men in their thirties reported this—again higher than any other age group.

The researchers say that “these findings are consistent with a picture whereby MSM on average pass HIV to men younger than themselves”.

However for all of these sexual risk behaviours, the age group least likely to report them was the oldest, those over the age of 50.

**Strategic positioning**
‘Strategic positioning’ refers to men choosing their sexual role with some consideration of what they believe to be their own HIV status and that of their partner. These decisions generally assume that HIV transmission occurs more frequently from the insertive to the receptive partner than the other way round.

As has been reported in previous surveys, men who had tested negative or who had never tested were much less likely to take the receptive role in unprotected anal intercourse if they knew their partner was HIV positive. Similarly, when men with diagnosed HIV were with a partner who they knew also had HIV, they were equally likely to have receptive or insertive unprotected sex. If they thought their partner was HIV-negative, they were much more likely to take the receptive role themselves.

But the survey also asked about positioning in relation to oral sex and ejaculation in the mouth, a previously unexplored area. Of all men who had had sex in the past year, 99.2% had had oral sex and 77% had had oral sex involving ejaculation in the mouth. But some men are giving attention to the HIV status of their partners in relation to this practice. For example, among HIV-positive men, ejaculation in a negative man’s mouth was much less common (13%) than having a negative man ejaculate in their mouth (26%).

**Condom failure**
Thirteen per cent of men who had used condoms in the past year had experienced a condom splitting or coming off during sex. The researchers asked about eight behaviours which are thought to increase the risk of this happening.

- 17% of condom users had used saliva as a lubricant. These men were somewhat more likely than other men to experience condom failure (odds ratio 1.32; 95% confidence interval 1.02—1.71).
- 15% of condom users reported having intercourse for over 30 minutes without changing the condom. Men who did so were twice as likely as other men to experience condom failure (2.34; confidence interval 1.85—2.95).
- 11% did not use any lubricant at all. These men were almost twice as likely to experience condom failure (1.86; confidence interval 1.40—2.48).

Moreover men reporting three other behaviours also had a statistically significant increased risk of experiencing condom failure. These behaviours were using oil-based lubricant, using a condom that is too small, and unrolling the condom before putting it on.

However, contrary to received wisdom, two of the behaviours asked about were not significantly associated with condom failure. Men who reported putting lubricant inside the condom and men who reported not using ‘lots of’ lubricant were no more likely to experience condom failure than other men.

Younger men, and men who had sex with both men and women, were more likely to experience condom failure than other men.

**HIV testing**

Continuing the rising trend seen in recent years, 72% of men completing the survey had ever been tested for HIV. However, excluding those who had been diagnosed with HIV over a year ago, only 46% of men had been tested for HIV in the last 12 months. However the Health Protection Agency and other organisations recommend that gay men should test annually.

Whereas over three-quarters of men who had tested had done so most recently at a sexual health or genito-urinary medicine (GUM) clinic, relatively high numbers had done so at less traditional settings. Nine per cent had tested at a GP surgery, 5% at a private health care clinic and 4% at an HIV organisation. On the other hand, less than 1% had tested at hospital or by using a home testing kit.

As in previous surveys, living with diagnosed HIV was more common among men in London and in the North West of England, men with lower educational qualifications, men with higher numbers of male sexual partners (especially those with 30 or more a year) and black men and men of white ‘non-British’ ethnicities.

**European study**

Also released last month are preliminary results from the largest ever international study of the sexual health of gay and bisexual men. When the Gay Men’s Sex Survey was conducted in the UK in 2010, the same internet-based questionnaire was made available in 25 languages across Europe.

The researchers were taken aback by the high level of response, with a total of 180,988 men completing the survey. The response rate was particularly high in Germany, Switzerland, Luxembourg, Ireland, Portugal, Slovenia and Austria. It was lowest in Turkey, Moldova and Russia.

Levels of basic HIV knowledge were generally very high, with 93% already knowing five key facts about HIV.

Overall, around 35% had taken an HIV test in the previous twelve months. Testing for HIV in the last year was most common in Spain, Portugal, Belgium and France. It was least common in Lithuania, Finland, Slovenia, Croatia and Turkey. The researchers say that in some countries, such as Poland and Russia, the proportion of gay and bisexual men who are HIV-positive is considerably higher than in previous estimates.

Full results will be published in the autumn of 2011.

**References**


**Population Council’s new microbicides protect against HIV for 24 hours in monkeys**

Keith Alcorn

Published: 06 January 2011

Two microbicide gels each containing new agents that can prevent HIV infection protected female monkeys from vaginal infection with HIV for up to 24 hours after one application, US scientists report today in the journal PLoS One.

The research funded by the Population Council shows that a gel which combines zinc acetate and the non-nucleoside reverse transcriptase inhibitor MIV-150 protected rhesus macaques from HIV infection in every case if applied daily for two weeks, while application every other day for four weeks protected around three-quarters of the macaques from HIV infection.

Microbicides to prevent HIV infection are now a promising avenue of HIV prevention research following the results of the CAPRISA 004 trial, which showed that a microbicide gel containing the antiretroviral drug tenofovir reduced the risk of HIV infection for women by around 39%.
Antiretroviral agents from six antiretroviral drug classes are also under investigation for use in microbicides, including the non-nucleoside reverse transcriptase inhibitor dapivirine.

According to the study investigators, MIV-150 is less likely to lead to resistance than other agents of the NNRTI class, potentially making it suitable for use in a microbicide.

The investigators also tested zinc acetate, which has the potential to prevent HIV infection and also other sexually transmitted infections, such as HSV-2, the virus that causes genital herpes.

Both agents were tested individually and in combination with each other, and were delivered in a carageenan-based gel. Carrageenan is extracted from seaweed. The Population Council has previously tested a carageenan-based microbicide product, Carraguard, but found that although safe to use, it failed to protect women against HIV infection.

In this study researchers also looked at whether the products were effective when used a long time before HIV exposure. Most previous studies, in both animals and humans, have used products that were applied no more than a few hours before HIV exposure, so-called `coitally-dependent` application.

The need to apply a gel at the right time – no more than a few hours before intercourse takes place – may be one reason why almost all microbicide trials have shown that agents which look promising in the test tube or in animal studies tend not to protect against HIV infection when used by women in real-life conditions.

Good adherence – using a microbicide gel on the majority of occasion when vaginal intercourse takes place – was strongly associated with a lower risk of HIV acquisition in the CAPRISA 004 study, for example.

A `coitally independent` microbicide, which could be used each day, but at a time of the woman’s choosing rather than just before sexual intercourse, might be easier for women to use consistently. One approach already being investigated is the use of a ring lodged at the cervix to dispense an antiviral agent in the vagina for up to a month, but approaches using a long-acting gel may also be useful, particularly if that product can protect against a range of sexually transmitted infections.

The study reported this week shows that the gel containing MIV-150 has a long-lasting effect if it is applied daily for at least two weeks, even when a very low dose of the drug is used. This may be a result of MIV-150’s tendency to accumulate in tissues, particularly in the cervical tissue.

The risk of infection appeared to be correlated with concentrations of the drug in the cervical tissue, the researchers reported. They also say that they have observed that cells exposed to MIV-150 remain resistant to HIV infection for up to five days, although these data remain unpublished.

The risk of drug resistance as a result of using antiretroviral microbicides is a concern shared by many researchers, particularly in relation to drugs in common use for antiretroviral treatment of HIV-infected people in developing countries.

No trace of MIV-150 could be found in the blood, and no drug resistance could be detected in macaques that became infected despite dosing with the microbicide containing MIV-150.

The researchers refer to unpublished data showing that resistance to MIV-150 is slow to develop in comparison to other NNRTIs, and active against viruses resistant to nevirapine, currently the most commonly used NNRTI in developing countries.

However viruses resistant to efavirenz, the other NNRTI now coming into greater use in developing countries, may have some resistance to MIV-150. This suggests that a small risk exists that the microbicide might not protect against efavirenz-resistant HIV, and further tests will be needed to investigate this question.

When used alone, MIV-150 protected 56% of macaques challenged with SHIV eight hours after the last gel application and 11% of macaques challenged 24 hours after the last gel application.

When combined with zinc acetate, the combination gel protected all 21 macaques challenged with SHIV 24 hours after the last gel application, following two weeks of daily gel application. When the gel was applied every other day for four weeks, and seven macaques were then challenged 24 hours after the last application, 67% were protected against HIV infection.

Zinc acetate was also tested for its anti-HIV effect alone, and showed a strong protective effect, protecting 11 of 14 macaques from infection. When data from daily or every-other-day dosing were pooled, the protective effect was statistically significant (70%, p<0.02).

The Population Council now plans to test both the combination product and zinc acetate as microbicides against HIV infection in phase 1 human trials which could begin in early 2012. MIV-150 was developed by the Swedish company Medivir and licensed to the Population Council in 2003.

Kenya: Police Storm U.S. Army HIV Research Clinic
Tirop Benedict
5 January 2011
Nairobi — Police in Kericho stormed a United States Military HIV Research Programme clinic following claims that a minor had died there while donating blood.

The officers forced their way into the heavily guarded facility and searched the blood donation tents.

They found two women waiting for a medical check-up.

The officers, who were accompanied by Majengo Ward Councillor Elijah Ruto, later held talks with senior researchers at the facility.

On leaving they told journalists, who were barred from entering the clinic, that the death claims were false.

Police officers dispersed a crowd of onlookers milling around the facility.

A source, who requested anonymity as she was not authorised to talk to journalists, said the facility received hundreds of people who donate blood for research or to know their HIV status.

She disputed claims of people "selling blood", saying donors were adults who only did so after signing consent forms.

She added that blood donors were given Sh1,000 for transport back home "as most of them were quite sick and came from very poor backgrounds".

There have been allegations of a blood selling racket where brokers, who included commercial sex workers, lure girls to "donate" blood at the facility and then receive the "transport fees."

Efforts to get comments from the programme’s deputy director, Dr Fredrick Sawe, failed as he was said to be out of the office.

Another official referred the Nation to the Kenya Medical Research Institute under which the project falls.

The Walter Reed Project, Kericho HIV Programme is led by US Department of Defence and Kenyan medical professionals. It does research at five other military bases in Kenya.

The mission of the programme is to develop and test improved means for predicting, detecting, preventing and treating infectious disease in East Africa.

One in 10 Elderly Have Unsafe Sex
Korea Times (Seoul), (01.04.2011) Lee Hyo-sik

A survey of 1,804 Korean men and women age 60 and older suggests that seniors lack adequate knowledge of safe-sex practices and underestimate their risk for STD infection.

"With the rising life expectancy and improving health conditions, a growing number of senior citizens are seeking an active sex life," explained study authors Lee Seung-joo and Choi Hyun-seob, professors at the Urology Department at St. Vincent’s Hospital, which is affiliated with Catholic University of Korea.

The average age of survey participants was 64.6, and most resided in Seoul or other urban centers. Of the 816 men and 988 women, roughly 26.2 percent said they did not ever use condoms for intercourse, while 28.6 percent said they did so only occasionally. Some 78.2 percent had not previously been screened for STDs.

Of respondents, 37.5 percent reported that they or their partners have taken Viagra or similar drugs. Around 10.6 percent of the men reported sex with a prostitute at least once within the past year.

"Given that an increasing number of senior citizens are engaging prostitutes, the government should make greater efforts to increase the awareness about the risk of unprotected sex and properly treat senior citizens infected with STDs," said Choi.

South Korean Health Ministry data show that STD cases among those 65 and older increased from 44,000 in 2007 to 64,000 in 2009. Seniors accounted for 5.5 percent of total STD patients in 2009, up from 4 percent three years ago.

AIDS Gel Prevents Infection in Monkeys

Reuters, (01.05.2011) Maggie Fox

An experimental vaginal microbicide applied daily protected female monkeys against simian HIV (SHIV) infection, even hours after application, according to the authors of a new study.

The gel combines zinc acetate and micromolar doses of MIV-150, a novel non-nucleoside reverse transcriptase inhibitor. Researchers tried using a gel containing each ingredient by itself, but they found the combination provided the best protection against SHIV.

The combination gel “afforded full protection (21 of 21 animals) for up to 24 hours after two weeks of daily application,” wrote Melissa Robbiani, of the Population Council, and colleagues. The council led the study and holds a license to MIV-150, which was developed by Sweden-based Medivir.

The small dose of active drug in the gel might boost its safety profile and keep it cheap, the Population Council noted. The zinc acetate is meant to help prevent herpes, but that benefit was not tested in this trial. It also does not prevent pregnancy, though the researchers are working on a combination gel or ring that could be contraceptive.

“Just the idea of having a product that a woman could use to address the issue of unplanned pregnancy and [STDs] as well, that would be an enormous benefit to women,” said Bethany Young Holt, a microbicide expert and director of the Coalition Advancing Multipurpose Innovations, a women’s health research and advocacy group.

In addition to the Population Council, the National Cancer Institute and other labs helped test the gel.

The study, “An Antiretroviral/Zinc Combination Gel Provides 24 Hours of Complete Protection Against Vaginal SHIV Infection in Macaques,” was published in the open-access Public Library of Science-ONE (2011;6(1):e15835).

Abbott's Kaletra HIV Drug Patent Rejected in India, Allowing Cipla Copies


India’s patent office has refused Abbott Laboratories' application for copyright protection of its AIDS drug Kaletra, a decision that allows generic drug makers to continue selling copies of the medication. In ruling against Abbott’s request, the patent board found that the steps involved in manufacturing Kaletra “do not constitute an invention.” Indian drug makers Cipla Ltd. and Matrix Laboratories Ltd., as well as the Initiative for Medicines, Access & Knowledge, had challenged Abbott’s application. Abbott is reviewing the decision to determine its next steps, said company spokesperson Scott Stoffel.

Plastic Bags Not a Wise Substitute for Condoms: Ministry

The Nation (Bangkok), (01.05.2011)

Thailand’s Public Health Ministry is warning teenagers not to use plastic bags as a substitute for condoms. The practice, which a survey showed some youths in the nation's northeast have adopted, could lead to STDS as well as to genital injury and infection, the ministry said. The ministry distributes more than 20 million condoms a year to the public, including through volunteers and primary care units in villages. About 5 million condoms a year are purchased from some 20,000 vending machines the ministry has installed in public spaces. Efforts to raise awareness of condom use and pregnancy prevention among young people will be accelerated, said Public Health Minister Jurin Laksanawisit.

Bacteria Eyed for Possible Role in Atherosclerosis

ScienceDaily (Jan. 6, 2011) — Dr. Emil Kozarov and a team of researchers at the Columbia University College of Dental Medicine have identified specific bacteria that may have a key role in vascular pathogenesis, specifically atherosclerosis, or what is commonly referred to as “hardening of the arteries”—the number one cause of death in the United States.

Fully understanding the role of infections in cardiovascular diseases has been challenging because researchers have previously been unable to isolate live bacteria from atherosclerotic tissue. Using tissue specimens from the Department of Surgery and the Herbert Irving Comprehensive Cancer Center at Columbia University, Dr. Kozarov and his team, however, were able to isolate plaques from a 78-year-old male who had previously suffered a heart attack. Their findings are explained in the latest Journal of Atherosclerosis and Thrombosis.

In the paper, researchers describe processing the tissue using cell cultures and genomic analysis to look for the presence of culturable bacteria. In addition, they looked at five pairs of diseased and healthy arterial tissue. The use of cell cultures aided in the isolation of the bacillus Enterobacter hormaechei from
the patient's tissue. Implicated in bloodstream infections and other life-threatening conditions, the isolated bacteria were resistant to multiple antibiotics. Surprisingly, using quantitative methods, this microbe was further identified in very high numbers in diseased but not in healthy arterial tissues.

The data suggest that a chronic infection may underlie the process of atherosclerosis, an infection that can be initiated by the systemic dissemination of bacteria though different "gates" in the vascular wall—as in the case of a septic patient, through intestinal infection. The data support Dr. Kozarov's previous studies, where his team identified periodontal bacteria in carotid artery, thus pointing to tissue-destructing periodontal infections as one possible gate to the circulation.

Bacteria can gain access to the circulation through different avenues, and then penetrate the vascular walls where they can create secondary infections that have been shown to lead to atherosclerotic plaque formation, the researchers continued. "In order to test the idea that bacteria are involved in vascular pathogenesis, we must be able not only to detect bacterial DNA, but first of all to isolate the bacterial strains from the vascular wall from the patient," Dr. Kozarov said.

One specific avenue of infection the researchers studied involved bacteria getting access to the circulatory system via internalization in white blood cells (phagocytes) designed to ingest harmful foreign particles. The model that Dr. Kozarov's team was able to demonstrate showed an intermediate step where Enterobacter hormaechei is internalized by the phagocytic cells, but a step wherein bacteria are able to avoid immediate death in phagocytes. Once in circulation, Dr. Kozarov said, bacteria using this "Trojan horse" approach can persist in the organism for extended periods of time while traveling to and colonizing distant sites. This can lead to multitude of problems for the patients and for the clinicians: failure of antibiotic treatment, vascular tissue colonization and initiation of an inflammatory process, or atherosclerosis, which ultimately can lead to heart attack or stroke.

"Our findings warrant further studies of bacterial infections as a contributing factor to cardiovascular disease, and of the concept that 'bacterial persistence' in phagocytic cells likely contributes to systemic dissemination," said Dr. Kozarov, an associate professor of oral biology at the College of Dental Medicine. Dr. Jingyue Ju, co-author and director of the Columbia Center for Genome Technology & Bio-molecular Engineering, also contributed to this research, which was supported in part by a grant from the National Heart, Lung, and Blood Institute of the National Institutes of Health and by the Columbia University Section of Oral and Diagnostic Sciences.

By Richard P. Grant

**Basophil Roles**

Dr. David Phillips/Visuals Unlimited, Inc.

**The paper**


**The finding**

Basophils were deemed critical in allergic response and parasite removal, but their precise role has been controversial. David Vöhringer, now at Universitätssklinikum Erlangen, found that basophils are not involved in the primary response against infection with parasitic worms (helminths), as researchers assumed, but rather play a role in immunological memory.

**The lucky break**

Type 2 helper T cells (Th2) cells secrete IL-4, which promotes B-cell production of antibodies essential for the removal of helminths. Basophils also release IL-4, so Vöhringer wondered if basophils might act coordinately with Th2 cells. He started by trying to conditionally remove a protease that was specific to basophils. Luckily, the engineered mice were unable to make basophils at all, thus providing the researchers with a model for studying basophil immunology.

**The mouse**

Vöhringer's mice could mount a perfectly adequate Th2 response to parasites, indicating that basophils weren't needed for instigating the antibody response. It suggested that basophils, "are not as sweepingly essential as first claimed," says Faculty Member Rick Maizels. Surprisingly, though, the mice failed to clear re-infections with parasites, suggesting that basophils are required for Th2–mediated immunological memory.
The next step
Now, Vöhringer is looking for the mechanism by which basophils contribute to long-term immunological memory and trying to identify which type of B cell interacts with basophils.

**Male Circumcision Helps Reduce Rates Of HPV Transmission To Women, Study Finds**
"Among HIV-negative sexual partners, male circumcision helps prevent the transmission of human papillomavirus [HPV] from men to women," according to a study published online Thursday in the Lancet, HealthDay News/Bloomberg Businessweek reports. "However, circumcision offers only partial protection and partners must still practice safe sex, the researchers pointed out," according to the news service (1/6).

Among other things, HPV infection can lead to cervical cancer in women, according to the authors of the study. "More than 85% of the HPV disease burden is in developing countries, and cervical cancer is the leading cause of cancer mortality in women in east Africa," they wrote. Though previous studies showed that male circumcision can protect men from HIV/AIDS and HPV, whether male circumcision protected women from HPV was previously unknown (Wawer et al., 1/7).

For the study, researchers "analyzed data from two clinical trials in Uganda that followed HIV-negative men and their HIV-negative female partners between 2003 and 2006," HealthDay News/Bloomberg Businessweek continues (1/6). The researchers "were able to get details on HPV infections for nearly 1,000 of the women, all identified by men as long-term sex partners such as wives," Reuters reports. "After two years, 27.8 percent of the steady partners of circumcised men had HPV infections, compared to 38.7 percent of the partners of uncircumcised men," the news service adds (Fox, 1/6).

Incidence of high-risk HPV infection, those infections that could lead to cancer, "was 23 percent lower for women with circumcised partners than for those with uncircumcised partners, the investigators found," HealthDay News/Bloomberg Businessweek adds (1/6). "Along with previous trial results in men, these findings indicate that male circumcision should now be accepted as an efficacious intervention for reducing heterosexually acquired high-risk and low-risk HPV infections in men who do not have HIV and in their female partners," the authors of the study write, according to according to a Lancet press release. "However, our results indicate that protection is only partial; the promotion of safe sex practices is also important," the add (1/6).

As MedPage Today reports, the authors note "the study did not assess cervical neoplasia directly," which is the presence of abnormal cervical cells. Additionally, the researchers "cautioned that [due to the fact the] men and women in the study were in stable relationships and did not have HIV at baseline, ... the results may not apply to other populations. The analysis may also have underestimated incidence, they cautioned, because infections acquired and cleared between the yearly follow-up points would have been missed," the news service writes (Smith, 1/6).

Still, the "findings add important evidence for the promotion of male circumcision in countries without well-established programmes for cervical screening," wrote the authors of an accompanying Lancet Comment. "Additional interventions to reduce HPV infection, such as provision of vaccines for HPV prevention, will be essential to reduce invasive cervical cancer worldwide. Male circumcision is associated with slight reductions in high-risk HPV, while licensed HPV vaccines protect with high effectiveness against only a limited number of HPV types. Therefore the two interventions are likely to have important synergistic effects" (Giuliano et al., 1/7).

**U.N. Announces Members Of Independent Panel To Investigate Source Of Haiti’s Cholera Epidemic**
U.N. Secretary-General Ban Ki-moon announced the names of four experts to be part of an independent panel that will "investigate the source of Haiti’s cholera epidemic, which some Haitians blame on U.N. peacekeepers," Reuters reports (Worsnip, 1/6). "The members of the panel have been selected based on their global stature, expertise and extensive experience working with cholera in all its aspects," according to a statement from Ban’s spokesperson, U.N. News Centre reports (1/6). "The panel will operate completely independently from the United Nations and will have access to all U.N. records, reports, facilities, and staff members as required. It will present a written report of its findings to the Secretary-General and to the Government of Haiti," the statement declares (1/6).

"The panel will be chaired by Alejandro Cravioto of Mexico, from the International Center for Diarrhoeal Disease Research in Bangladesh. The other three members are Claudio Lanata of the Instituto
de Investigacion Nutritional in Peru, Daniele Lantagne of Harvard University in the United States, and Balakrish Nair of the National Institute of Cholera and Enteric Diseases in India," according to U.N. News Centre (1/6).

In related news, Elisabeth Byrs, a spokesperson for the U.N. Organisation for the Coordination of Humanitarian Affairs (OCHA), "on Thursday blasted the response to an appeal to counter the deadly cholera epidemic in Haiti as 'shameful' after the world body received only a quarter of the funding it needs," Agence France-Presse reports.

"Out of the 174 million dollars (131 million euros), the U.N. has only received 44 million or 25 percent of the funds we asked for, although (the situation) is of the utmost urgency," Byrs said. "It's not moving. It's shameful that we should have so little money for an illness that currently kills in a flash because people don't have rehydration salts," she added.

OCHA made an appeal for donations to fight the cholera epidemic in November, the news service notes. "Byrs insisted there was still a need for speed and underlined that cholera could easily be treated when patients received enough care. The funding would also help to prevent waterways being contaminated and to set up more treatment centres in rural areas," AFP reports. According to figures from Haiti's health ministry last week, 3,333 people have died from the cholera epidemic and 150,000 have been infected (1/6).

Meanwhile The Economist looks at efforts to rebuild Haiti almost one year since the earthquake hit. "[W]hen visiting journalists parachute in to Port-au-Prince for the anniversary of the earthquake, they will see few signs of progress and many of stasis. Rubble still blocks many streets. Even if the work of removing it goes according to the official schedule, less than half will be cleared by October. Only about 30,000 temporary shelters have been built. ... This landscape of neglect and degradation mocks the widespread hope in the weeks after the quake that Haiti could 'build back better,'" as Bill Clinton, the United Nations special envoy to the country, put it," the magazine writes.

In describing the work of the Interim Haiti Reconstruction Commission (IHRC), The Economist writes that "it has met rarely, its mandate expires in nine months, and at its fourth meeting in December the 12 Haitian members complained in a letter that they felt left out." Pamela Cox, a World Bank official who sits on the IHRC, notes that even wealthy countries have struggled after disasters, pointing to Hurricane Katrina as an example. "Although she concedes that planning for reconstruction should have started earlier, Ms Cox says she sees progress: 400,000 houses have been assessed and classified by structural engineers, debris removal is accelerating and the economy has held up," the magazine reports.

The article also looks at how the ongoing presidential election fits into the rebuilding effort (1/6).

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How the case against the MMR vaccine was fixed **** (long)
Brian Deer, journalist

In the first part of a special BMJ series, Brian Deer exposes the bogus data behind claims that launched a worldwide scare over the measles, mumps, and rubella vaccine, and reveals how the appearance of a link with autism was manufactured at a London medical school

When I broke the news to the father of child 11, at first he did not believe me. “Wakefield told us my son was the 13th child they saw,” he said, gazing for the first time at the now infamous research paper, which linked a purported new syndrome with the measles, mumps, and rubella (MMR) vaccine. There’s only 12 in this.”

That paper was published in the Lancet on 28 February 1998. It was retracted on 2 February 2010. Authored by Andrew Wakefield, John Walker-Smith, and 11 others from the Royal Free medical school, London, it reported on 12 developmentally challenged children and triggered a decade long public health scare.

“Onset of behavioural symptoms was associated with the parents with measles, mumps, and rubella vaccination in eight of the 12 children,” began the paper’s “findings.” Adopting these claims as fact, its “results” section added: “In these eight children the average interval from exposure to first behavioural symptoms was 6.3 days (range 1-14).”
Mr 11, an American engineer, looked again at the paper: a five page case series of 11 boys and one girl, aged between 3 and 9 years. Nine children, it said, had diagnoses of “regressive” autism, and all but one were reported with “non-specific colitis.” The “new syndrome” brought these together, linking brain and bowel diseases. His son was the penultimate case.

Running his finger across the paper’s tables, over coffee in London, Mr 11 seemed reassured by his anonymised son’s age and other details. But then he pointed at table 2—headed “neuropsychiatric diagnosis”—and for a second time objected.

“That’s not true.”

Child 11 was among the eight whose parents apparently blamed MMR. The interval between his vaccination and the first “behavioural symptom” was reported as 1 week. This symptom was said to have appeared at age 15 months. But his father, whom I had tracked down, said this was wrong.

“From the information you provided me on our son, who I was shocked to hear had been included in their published study,” he wrote to me, after we met again in California, “the data clearly appeared to be distorted.”

He backed his concerns with medical records, including a Royal Free discharge summary. Although the family lived 5000 miles from the hospital, in February 1997 the boy (then aged 5) had been flown to London and admitted for Wakefield’s project, the undisclosed goal of which was to help sue the vaccine’s manufacturers.

**Wakefield’s “syndrome”**

Unknown to Mr 11, Wakefield was working on a lawsuit for which he sought a bowel-brain “syndrome” as its centrepiece. Claiming an undisclosed £150 (€180, $230) an hour through a Norfolk solicitor named Richard Barr, he had been confidentially put on the payroll two years before the paper was published, eventually grossing him £435 643, plus expenses.

Curiously, however, Wakefield had already identified such a syndrome before the project which would reputedly discover it. “Children with enteritis/disintegrative disorder [an expression he used for bowel inflammation and regressive autism] form part of a new syndrome,” he and Barr explained in a confidential grant application to the UK government’s Legal Aid Board before any of the children were investigated. “Nonetheless the evidence is undeniably in favour of a specific vaccine induced pathology.”

The two men also aimed to show a sudden-onset “temporal association”—strong evidence in product liability. “Dr Wakefield feels that if we can show a clear time link between the vaccination and onset of symptoms,” Barr told the legal board, “we should be able to dispose of the suggestion that it’s simply a chance encounter.”

But child 11’s case must have proved a disappointment. Records show his behavioural symptoms started too soon. “His developmental milestones were normal until 13 months of age,” notes the discharge summary. “In the period 13–18 months he developed slow speech patterns and repetitive hand movements. Over this period his parents remarked on his slow gradual deterioration.”

That put the first symptom two months earlier than reported in the *Lancet*, and a month before the boy received the MMR vaccination. And this was not the only anomaly to catch the father’s eye. What the paper reported as a “behavioural symptom” was noted in the records as a chest infection.

“Please let me know if Andrew W has his doctor’s license revoked,” wrote Mr 11, who is convinced that many vaccines and environmental pollutants may be responsible for childhood brain disorders. “His misrepresentation of my son in his research paper is inexcusable. His motives for this I may never know.”

The father need not have worried. My investigation of the MMR issue exposed the frauds behind Wakefield’s research. Triggering the longest ever UK General Medical Council fitness to practise hearing, and forcing the *Lancet* to retract the paper, last May it led to Wakefield and Walker-Smith being struck off the medical register.

Lawsuit test case

But Mr 11 was not the first parent with a child in the study whom I interviewed during my inquiries. That was Mrs 2: the first of the parents to approach Wakefield. She was sent to him by an anti-vaccine campaign called JABS. Her son had regressive autism, longstanding problems with diarrhoea, and was the prime example of the purported bowel and brain syndrome—still unsubstantiated.
This boy would appear in countless media reports, and was one of the four “best” cases in Barr’s lawsuit.

I travelled to the family home, 80 miles northeast of London, to hear about child 2 from his mother. That was in September 2003, when the lawsuit fell apart after counsel representing 1500 families said that, on the evidence, Barr’s autism claims would fail. By that time, Mrs 2 had seen her son’s medical records and expert reports written for her case at trial.

Her concerns about MMR had been noted by her general practitioner when her son was 6 years old. But she told me the boy’s troubles began after his vaccination, which he received at 15 months. “He’d scream all night, and he started head banging, which he’d never done before,” she explained.

“When did that begin, do you think?” I asked.

“That began after a couple of months, a few months afterward, but it was still, it was concerning me enough, I remember going back . . .”

“Sorry. I don’t want to be, like, massively pernickety, but was it a few months, or a couple of months?” “It was more like a few months because he’d had this, kind of, you know, slide down. He wasn’t right. Before he started.”

“Not quicker than two months, but not longer than how many months? What are we talking about here?”

“From memory, about six months, I think.”

The next day, she complained to my editors. She said my methods “seemed more akin to the gutter press.” But I was perplexed by her story, since there was no case in the Lancet that matched her careful account.

According to the paper, child 2 had his “first behavioural symptom” two weeks, not six months, after MMR. This was derived from a Royal Free history (citing “headbanging” and “screaming” as the start) taken by Mark Berelowitz, a child psychiatrist and a coauthor of the paper. He saw Mrs 2 during the boy’s admission, at age 8, after she had discussed her son’s story with Wakefield.

As I later discovered, each family in the project was involved in such discussions before they saw the hospital’s clinicians. Wakefield phoned them at home, and must have at least suggestively questioned them, potentially impacting on later history taking. But I knew little of such things then, and shared my confusion with Walker-Smith, whom I met shortly after Mrs 2.

“There is no case in the paper that is consistent with the case history [Mrs 2] has given me,” I told him. “There just isn’t one.”

“Well that could be true,” the former professor of paediatric gastroenterology replied, disarmingly. He knew the case well, having admitted the boy for the project and written reports for Barr, who paid him £23,000.

“Well, so either what she is telling me is not accurate, or the paper’s not accurate.”

“Well I can’t really comment,” he said. “You really touch on an area which I don’t think should be debated like this. And I think these parents are wrong to discuss such details, where you could be put in a position of having a lot of medical details and then try to match it with this, because it is a confidential matter.”

It was not merely medically confidential, it was also legally protected: a double screen against public scrutiny. But responding to my first MMR reports, in the Sunday Times in February 2004, the GMC decided to investigate the cases and requisitioned the children’s records.

The regulator’s main focus was whether the research was ethical. Mine was whether it was true. So as a five member disciplinary panel trawled through the records, with five Queen’s counsel and three defendant doctors, I compared them with what was published in the journal.

**Multiple discrepancies**

The paper gave the impression that the authors had been scrupulous in documenting the patients’ cases. “Children underwent gastroenterological, neurological, and developmental assessment and review of developmental records,” it explained, specifying that Diagnostic and Statistical Manual of Mental Disorders IV criteria were used for neuropsychiatric diagnoses. “Developmental histories included a review of prospective developmental records from parents, health visitors, and general practitioners.”

But, when the details were dissected before the GMC panel, multiple discrepancies emerged. A syndrome necessarily requires at least some consistency, but, as the records were laid out, Wakefield’s crumbled.
First to crack was “regressive autism,” the bedrock of his allegations. 38 39 “Bear in mind that we are dealing with regressive autism in these children, not of classical autism where the child is not right from the beginning,” he later explained, for example, to a United States congressional committee. 40

But only one—child 2—clearly had regressive autism. 41 Three of nine so described clearly did not. None of these three even had autism diagnoses, either at admission or on discharge from the Royal Free.

The paper did not reveal that two of this trio were brothers, living 60 miles south of the hospital. Both had histories of fits and bowel problems 42 recorded before their MMR vaccinations. 43 44 The elder, child 6, aged 4 years at admission, had Asperger’s syndrome, 45 which is distinct from autism under DSM-IV, is not regressive. 46 and was confirmed on discharge. 47 His brother, child 7, was admitted at nearly 3 years of age without a diagnosis 48 and a post-discharge letter from senior paediatric registrar and Lancet coauthor David Casson 49 summarised: “He is not thought to have features of autism.” 50

The third in the trio, child 12, was enrolled on the advice of the brothers’ mother—reported in media to be a JABS activist, and who had herself “only relatively recently” 51 blamed the vaccine. Child 12 was aged 6 at admission and had previously been assessed for possible Asperger’s syndrome at Guy’s Hospital, London, by a renowned developmental paediatrician. 52 53 She diagnosed “an impairment in respect of language”—an opinion left undisturbed by Berelowitz. 54 55

Mrs 12 was a GMC witness at its mammoth hearing, which between July 2007 and May 2010 ran for 217 days. She explained that the brothers’ mother had made her suspicious of MMR and had given her Barr’s and Wakefield’s names. 56 Mrs 12 then approached them and filed a statement for legal aid before her son was referred. 57

“It was like a jigsaw puzzle—it suddenly seemed to fit into place,” she told the panel, describing how she concluded, four years after the boy was vaccinated, that MMR was to blame for his problems. “I had this perfectly normal child who, as I could see, for no apparent reason started to not be normal.”

The 12 children were admitted between July 1996 and February 1997, and others had connections not revealed in the paper, almost as striking as the trio’s. The parents of child 9 and child 10 were contacts of Mrs 2, who ran a group that campaigned against MMR. 58 And child 4 and child 8 were admitted—without outpatient appointments 59—for ileocolonoscopy and other invasive procedures, from one Tyneside general practice, 280 miles from the Royal Free, after advice from anti-MMR campaigners. 60

Pre-existing problems
Both child 4 and child 8 were among the eight whose parents were reported to have blamed the vaccine. But although the paper specified that all 12 children were “previously normal,” 61 both had developmental delays, and also facial dysmorphisms, noted before MMR vaccination.

In the case of child 4, who received the vaccine at age 4 years, Wakefield played down problems, suggesting that early issues had resolved. “Child four was kept under review for the first year of life because of wide bridging of the nose,” he reported in the paper. “He was discharged from follow-up as developmentally normal at age 1 year.”

But medical records, presented by the GMC, give a different picture for this child. Reports from his pre-MMR years were peppered with “concerns over his head and appearance,” 62 “recurrent” diarrhoea, 63 “developmental delay,” 64 “general delay,” and restricted vocabulary. 65 And although before his referral to Wakefield his mother had inquired about vaccine damage compensation, 66 his files include a report of a “very small deletion within the fragile X gene,” 67 and a note of the mother’s view that her concerns about his development had begun when he was 18 months old. 68

“In general, his mother thinks he developed normally initially and subsequently his problems worsened, and he lost some of his milestones, but he subsequently improved on a restrictive exclusion diet,” wrote his general practitioner, William Tapsfield, referring the boy, then aged 9, after a phone conversation with Wakefield. “The professionals who have known [child 4] since birth don’t entirely agree with this, however, and there is a suggestion that some of his problems may have started before vaccination.” 69

Similarly with child 8, who was also described in the Lancet as having overcome problems recorded before vaccination. “The only girl . . . was noted to be a slow developer compared with her older sister,” the paper said. “She was subsequently found to have coarctation of the aorta. After surgical repair of the aorta at the age of 14 months, she progressed rapidly, and learnt to talk. Speech was lost later.”

But Wakefield was not a paediatrician. He was a former trainee gastrointestinal surgeon with a non-clinical medical school contract. 70 And his interpretation differed from that of local consultants (including a developmental paediatrician and a geneticist) who had actually looked after the girl. Her doctors put the coarctation side by side with the delay and dysmorphism, 71 and noted of her vocabulary that, before MMR at 18 months, she vocalised only 72 “two or three words.” 73
“[Child 8’s] mother has been to see me and said you need a referral letter from me in order to accept child 8 into your investigation programme,” the general practitioner, Diana Jelley, wrote to Wakefield at referral, when the girl was aged 3 and a half years. “I would simply re-iterate . . . that both the hospital and members of the primary care team involved with [child 8] had significant concerns about her development some months before she had her MMR.”

The girl’s general practice notes also provide insight into the background to the 12 children’s referrals. After person(s) unknown told Mrs 8 that her daughter may have inflammatory bowel disease, Jelley wrote: “Mum taking her to Dr Wakefield, Royal Free Hospital for CT scans/gut biopsies? Crohn’s—will need ref letter—Dr W to phone me. Funded through legal aid.”

**The child was “pale”**

The remaining five children served Wakefield’s claims no better. There was still no convincing MMR syndrome. Child 1, aged 3 years when he was referred to London, lived 100 miles from the Royal Free, and had an older brother who was diagnosed as autistic. Child 1’s recorded story began when he was aged 9 months, with a “new patient” note by general practitioner Andrea Barrow. One of the mother’s concerns was that he could not hear properly—which might sound like a hallmark presentation of classical autism, the emergence of which is often insidious. Indeed, a Royal Free history, by neurologist and coauthor Peter Harvey, noted “normal milestones” until “18 months or so.”

Child 1 was vaccinated at 12 months of age, however. Thus neither 9 nor 18 months helped Wakefield’s case. But in the *Lancet*, the “first behavioural symptom” was reported “1 week” after the injection, holding the evidence for the lawsuit on track.

Step 1 to achieve this: two and a half years after the child was vaccinated, Walkerk-Smith took an outpatient history. Although the mother apparently had no worries following her son’s vaccination, the professor elicited that the boy was “pale” 7-10 days after the shot. He also elicited that the child “possibly” had a fever, and “may” have been delirious, as well as pale.

“It’s difficult to associate a clear historical link with the MMR and the answer to autism,” Walker-Smith wrote to the general practitioner, with a similar letter to Wakefield, “although [Mrs 1] does believe that [child 1] had an illness 7-10 days after MMR when he was pale, ?fever, ?delirious, but wasn’t actually seen by a doctor.”

Step 2: for the *Lancet*, Wakefield dropped the question marks, turning Walker-Smith’s queries into assertions. And, although Royal Free admission and discharge records refer to “classical” autism, step 3, the former surgeon reported “delirium” as the first “behavioural symptom” of regressive autism, with, step 4, a “time to onset” of 7 days.

So here—behind the paper—is how Wakefield evidenced his “syndrome” for the lawsuit, and built his platform to launch the vaccine scare.

“It is significant that this syndrome only appeared with the introduction of the polyvalent MMR vaccine in 1988 rather than with the monovalent measles vaccine introduced in 1968,” he claimed in one views about the effect of vaccines on the nation’s children,” Barr said. “He is also anxious to arrange for...
tests to be carried out on any children . . . who are showing symptoms of possible Crohn’s disease. The following are signs to look for. If your child has suffered from all or any of these symptoms could you please contact us, and it may be appropriate to put you in touch with Dr Wakefield.”

The listed symptoms included pain, weight loss, fever, and mouth ulcers. Clients and contacts were quickly referred. Thus, an association between autism, digestive issues, and worries about MMR—the evidence that launched the vaccine scare—was bound to be found by the Royal Free’s clinicians because this was how the children were selected.

Moreover, through the omission from the paper of some parents’ beliefs that the vaccine was to blame, the time link for the lawsuit sharpened. With concerns logged from 11 of 12 families, the maximum time given to the onset of alleged symptoms was a (forensically unhelpful) four months. But, in a version of the paper circulated at the Royal Free six months before publication, reported concerns fell to nine of 12 families but with a still unhelpful maximum of 56 days. Finally, Wakefield settled on 8 of 12 families, with a maximum interval to alleged symptoms of 14 days.

Between the latter two versions, revisions also slashed the mean time to alleged symptoms—from 14 to 6.3 days. “In these children the mean interval from exposure to the MMR vaccine to the development of the first behavioural symptom was six days, indicating a strong temporal association,” he emphasised in a patent for, among other things, his own prophylactic measles vaccine, eight months before the Lancet paper.

This leaves child 3. He was 6½ and lived on Merseyside: 200 miles from the hospital. He received MMR at 14 months, with the first concerns recorded in the general practitioner’s notes 15 months after that. His mother—who 4 years later contacted Wakefield on the advice of JABS—told me that her son had become aggressive towards a brother, and records say that his vocabulary had not developed.

“We both felt that the MMR needle had made [child 3] go the way he is today,” the parents wrote to a local paediatric neurologist, Lewis Rosenbloom, 18 months before their son’s referral to London. They told him they wanted “justice” from the vaccine’s manufacturer, and that they had been turned down for legal aid. “Although it is said that the MMR has never been proven to make children to be autistic, we believe that the injection has made [child 3] to be mentally delayed, which in turn may have triggered off the autism.”

I visited this family twice. Their affected son was now a teenager and a challenge both to himself and to others. His mother said his diagnosis was originally “severe learning difficulties with autistic tendencies” but that she had fought to get it changed to autism.

As for a connection with MMR, there was only suspicion. I do not think his family was sure, one way or the other. When I asked why they took him to the Royal Free, his father replied: “We were just vulnerable, we were looking for answers.”

What was unquestionably true was that child 3 had serious bowel trouble: intractable, lifelong, constipation. This was the most consistent feature among the 12 children’s symptoms and signs but, being the opposite of an expected finding in inflammatory bowel disease, it was nowhere mentioned in the paper. This young man’s was so severe that he was dosed at his special school, his mother said, with up to five packets of laxative a day.

“You always knew when his stomach was hard,” she told me, in terms echoed over the years by many parents involved with Wakefield. “He would start headbutting, kicking, breaking anything in the house. Then he would go to the toilet and release it.”

For the Royal Free team, however, when reporting on these patients, such motility issues were sidelined in the hunt for Wakefield’s syndrome. In almost all the children, they noted commonly swollen glands in the terminal ileum, and what was reported as “non-specific colitis.” In fact, as I revealed in the BMJ last April, the hospital’s pathology service found the children’s colons to be largely normal, but a medical school “review” changed the results.

In this evolution of the gut pathology noted in the records to what was published in the paper, child 3’s case is a prime example. After ileocolonoscopy (which, GMC prosecution and defence experts agreed, was not clinically indicated), the hospital’s pathologists found all colonic samples to be “within normal histological limits”. But three months after the boy was discharged, Walker-Smith recalled the records and changed the diagnosis to “indeterminate ileocolitis”.

“I think, sadly, this was the first child who was referred, and the long term help we were able to give in terms of dealing with constipation was not there,” he told the GMC panel. “However, we had excluded Crohn’s disease and we had done our best to try and help this child, but in the end we did not.”
So that is the *Lancet* 12: the foundation of the vaccine scare. No case was free of misreporting or alteration. Taken together, NHS records cannot be reconciled with what was published, to such devastating effect, in the journal (table 4).

Comparison of three features of the 12 children in the *Lancet* paper with features apparent in the NHS records, including those from the Royal Free hospital

<table>
<thead>
<tr>
<th>Child no</th>
<th>Regressive autism</th>
<th>Non-specific colitis</th>
<th>First symptoms days after MMR</th>
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<td>1</td>
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<td>6/12</td>
</tr>
</tbody>
</table>

See supplementary data on bmj.com for a version of this table with detailed footnotes.

*Regressive developmental disorder—autism.
†Royal Free hospital pathology service.
‡First behavioural symptoms ≤14 days after MMR.

Comparison of three features of the 12 children in the *Lancet* paper with features apparent in the NHS records, including those from the Royal Free hospital.

Wakefield, however, denies wrongdoing, in any respect whatsoever. 119 He says he never claimed that the children had regressive autism, nor that he said they were previously normal. He never misreported or changed any findings in the study, and never patented a measles vaccine. None of the children were Barr’s clients before referral to the hospital, and he never received huge payments from the lawyer. There were no conflicts of interest. He is the victim of a conspiracy. 120 121 He never linked autism with MMR.

“Mr Deer’s implications of fraud against me are claims that a trained physician and researcher of good standing had suddenly decided he was going to fake data for his own enrichment,” he said in a now abandoned complaint against me to the UK Press Complaints Commission. “The other authors generated and ‘prepared’ all the data that was reported in the *Lancet*. I merely put their completed data in tables and narrative form for the purpose of submission for publication.”

But, despite signing up to claim credit for a paper in the *Lancet*, his co-authors Walker-Smith and Murch did not even know which case was which. Walker-Smith said he had “trusted” Wakefield. 122 “When I signed that paper, I signed with good intent,” he told the GMC panel. Denying any wrongdoing, he argued that the published report was not even about MMR, but merely described a new “clinicopathological entity”. He said that the admissions to the Royal Free were “entirely related to gastroenterological illness” and how the children were sourced was “irrelevant” and “immaterial.” His lawyers said that he was appealing against the panel’s decision and on these grounds they had advised him not to respond to my questions.

The journal, meanwhile, took 12 years to retract the paper, by which time its mischief had been exported. As parents’ confidence slowly returned in Britain, the scare took off around the world, unleashing fear, guilt, and infectious diseases—and fuelling suspicion of vaccines in general. In addition to measles outbreaks, other infections are resurgent, with Mr 11’s home state of California last summer seeing 10 babies dead from whooping cough, in the worst outbreak since 1958. 123

Wakefield, nevertheless, now apparently self-employed and professionally ruined, remains championed by a sad rump of disciples. “Dr Wakefield is a hero,” is how one mother caught their mood in a recent *Dateline NBC* TV investigation, featuring the story of the doctor and me. 124 “I don’t know where we would be without him.”

**How the link was fixed**

The *Lancet* paper was a case series of 12 child patients; it reported a proposed “new syndrome” of enterocolitis and regressive autism and associated this with MMR as an “apparent precipitating event.” But in fact:
• Three of nine children reported with regressive autism did not have autism diagnosed at all. Only one child clearly had regressive autism.
• Despite the paper claiming that all 12 children were “previously normal,” five had documented pre-existing developmental concerns.
• Some children were reported to have experienced first behavioural symptoms within days of MMR, but the records documented these as starting some months after vaccination.
• In nine cases, unremarkable colonic histopathology results—noting no or minimal fluctuations in inflammatory cell populations—were changed after a medical school “research review” to “non-specific colitis.”
• The parents of eight children were reported as blaming MMR, but 11 families made this allegation at the hospital. The exclusion of three allegations—all giving times to onset of problems in months—helped to create the appearance of a 14 day temporal link.
• Patients were recruited through anti-MMR campaigners, and the study was commissioned and funded for planned litigation.

Notes
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Footnotes
• Funding: Brian Deer’s investigation was funded by the Sunday Times of London and the Channel 4 television network. Reports by Deer in the BMJ were commissioned and paid for by the journal. No other funding was received, apart from legal costs paid to Deer by the Medical Protection Society on behalf of Andrew Wakefield.
• Competing interests: The author has completed the unified competing interest form at www.icmje.org/coi_disclosure.pdf (available on request from him) and declares no support from any organisation for the submitted work; no financial relationships with any organisation that might have an interest in the submitted work in the previous three years; BD’s investigation led to the GMC proceedings referred to in this report, including the charges. He made many submissions of information but was not a party or witness in the case, nor involved in its conduct.
• Provenance and peer review: Commissioned; externally peer reviewed.

1. References
4. One child, child 5, was admitted without any developmental diagnosis, but was in treatment for epilepsy.
5. Although the paper makes clear that the research did not prove an association between MMR and the purported syndrome, it describes its Table 2 as summarising “the apparent precipitating events; onset of behavioural features; and age of onset of both behaviour and bowel symptoms.”
7. Although Wakefield and the Lancet would later claim that the Legal Aid Board commissioned a quite separate “viral” study, the work specified in the documents submitted to the Legal Aid Board, seeking funding, on 6 June 1996, included clinical examination, ileocolonoscopy, histology, immunohistochemistry and molecular analysis for measles virus, neuropsychiatric studies, MRI brain scan, lumbar puncture, EEG and evoked potentials, B12 studies, modified Schilling test, and various blood and urine tests. The document includes costs, such as £1750 for colonoscopy with four night’s stay, £1000 for MRI scans, and £1400 for medical reports. Molecular, immunohistochemical, and electron microscopic analysis of tissues was priced at £500 per child. Named investigators for the legal project who would also be authors of the Lancet paper were Andrew Wakefield, John Walker-Smith, Simon Murch, David Casson, Amar Dhillon, John Linnell, Mark Berelowitz, and Peter Harvey. The document states: “The objective is to seek evidence which will be acceptable in a court of law of the causal connection between either the mumps, measles and rubella vaccine or the measles/rubella vaccine and certain conditions which have been reported with considerable frequency by families of children who are seeking compensation. It is hoped that using the testing protocol attached it will be possible to establish the causal link between the administration of the vaccines and the conditions outlined in this proposed protocol and costing proposal.” The board commissioned the project under an “authority to do contractual work,” naming Wakefield, issued on 22 August 1996. The technical specification is materially identical to a protocol submitted for approval by the Royal Free’s ethics committee, and the work to be performed is materially identical to the study submitted by Wakefield to the Lancet, with data sliced into two paired papers, which were peer reviewed together. One was published on 28 February 1998, and the other was rejected by the journal.
8. MMR and MR Vaccine Litigation Sayers and others v Smithkline Beecham plc and others—[2007] All ER (D) 30 (Jun).
9. Although some of his professional colleagues have admitted awareness of a relationship between Wakefield and the lawyer, his co-authors have denied any knowledge that he was contractually employed and funded by Barr. For example, in an email dated 27 February 2004, Walker-Smith wrote: “No financial details of Andy’s work was ever discussed with me by anyone and I was totally unaware of the grant of £55,000 that had been paid to him in an NHS Trust Fund, until Deer told me to my astonishment in December 2003.” Also in February 2004, John O’Leary, a Wakefield research collaborator and business partner, issued a statement to Deer, through lawyers: “We were not made aware, nor were we aware, of any liaison between Dr
Wakefield and Mr Richard Barr of Alexander Harris Solicitors that apparently existed since 1996. In addition, we had never been informed that the LSC [the Legal Services Commission, successor to the Legal Aid Board] had funded Dr Wakefield.”


The GMC panel examined records for all of the Lancet children except child 11. It also examined the records of an additional patient, child JS, a barr client who was denied by his paediatrician enrolment into the study, despite repeated requests from Wakefield and Walker-Smith. This boy was later admitted as a private patient and became a lead claimant, alongside child 2, in the lawsuit.

The third defendant was Simon Murch, at the time of these events consultant paediatric gastroenterologist at the Royal Free, and now professor of medicine at Warwick University. On 28 January 2010, he was found to have misled the Royal Free’s ethics committee, acted contrary to the clinical interests of children, and failed in his duties as a responsible consultant.

Kieran Coonan QC for Wakefield. Stephen Miller QC for Walker-Smith. Adrian Hopkins QC for Simon Murch. Sally Smith QC appeared for the GMC. The independent legal assessor, advising the panel, was Nigel Seed QC.

Andrew Wakefield. Evidence to the panel. Day 59. “Firstly, as with all other potential referrals, the parents had made contact with me and had described their child’s problems as they perceived them...” In some cases, he sent them documents setting out his theories and plans. Day 59. Although an academic researcher with no clinical duties, Wakefield was anxious to talk with parents before referral. For example, he wrote to family of child 4. Day 51. “Thank you very much for your letter regarding your son. I would be very grateful if you could phone me or my secretary with your telephone number so that we can discuss this directly.” He wrote to the parents of child 12. Day 42. “It will be necessary for me to discuss the nature of the referral with your GP and I would be grateful if you could let me have his/her name, telephone number. Also could you please let me have your telephone number so that I can speak to you directly on the subject.”


Panel findings of fact. Ten children (1, 2, 3, 5, 6, 7, 8, 9, 10, 12) were found to have been subjected to invasive investigations for research purposes without ethical approval. In seven cases (1, 2, 3, 5, 8, 9, 12) this was found to be contrary to the child’s clinical interests. Eight children (1, 2, 3, 5, 6, 7, 8, 9, 12) were caused to undergo gastroscopy which were not clinically indicated. Seven children (1, 2, 3, 5, 8, 9, 12) were caused to undergo barium meals and follow throughs which were not clinically indicated. Three children (3, 9, 12) were caused to undergo lumbar punctures which were not clinically indicated.

Interviewed by Brian Deer, both Mrs 2 and the organiser of JABS confirmed this.


Andrew Wakefield. Evidence to the panel. Day 59. “Firstly, as with all other potential referrals, the parents had made contact with me and had described their child’s problems as they perceived them...” In some cases, he sent them documents setting out his theories and plans. Day 59. Although an academic researcher with no clinical duties, Wakefield was anxious to talk with parents before referral. For example, he wrote to family of child 4. Day 51. “Thank you very much for your letter regarding your son. I would be very grateful if you could phone me or my secretary with your telephone number so that we can discuss this directly.” He wrote to the parents of child 12. Day 42. “It will be necessary for me to discuss the nature of the referral with your GP and I would be grateful if you could let me have his/her name, telephone number. Also could you please let me have your telephone number so that I can speak to you directly on the subject.”


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Sylvia Dean, lay member; Wendy Golding, lay member; Surendra Kumar, GP (chair); Parimala Moodley, psychiatrist; Stephen Webster, geriatrician.

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On 24 May 2010, Day 217, the panel noted that Murch’s involvement with the project was “subsidiary to and more limited” than Wakefield’s and Walker-Smith’s, that he had shown insight into his conduct, and had “demonstrated errors of judgment but had acted in good faith”. He was acquitted of serious professional misconduct.
39. Andrew Wakefield. Evidence to the panel. (a) Day 49. “Q: What did you understand that phrase to mean, ‘pilot study?’ A: This refers specifically and exclusively to the Legal Aid Board pilot study. That is, the investigation of five children with Crohn’s disease and five children with regressive autism and gastrointestinal symptoms.” (b) Day 52. “Q: The second aspect concerns the second box down, which is noted ‘Diagnosis’ and you see what you have written there: ‘Regressive autism + inflammatory bowel disease’. Again, what did you intend to convey by using that expression on this document? A: Based upon my understanding at the time, that was the likely diagnosis in this child.”
43. Dr N. GP records. Day 6.
49. Panel findings of fact. Page 93.
50. Repeated, multiple comparisons between Casson’s documentation shows an exceptional degree of concordance with clinical records generated by consultants.
52. John Walker-Smith. Outpatient history, taken from the mother. 2 October 1996. Day 41. “He had behaviour changes within a week, although the mother has only relatively recently associated the change of behaviour with MMR.”
53. Andrew Wakefield. Letter to Mrs 12. 19 July 1996. Day 28. “Thank you for your letter regarding your son. We have recently taken a profound interest in this subject, particularly in view of the link between bowel problems and Asperger’s Syndrome. I would greatly appreciate if you would mind calling me at the Royal Free before 3rd August and in addition I would like you to seek a referral from your GP to Professor John Walker-Smith, Professor of Paediatric Gastroenterology at the Royal Free Hospital, for investigation.”
55. Panel findings of fact. Page 34.
56. Michael Rutter, an expert witness for the GMC, said that there was “no evidence that I could identify” in the child’s records indicating any significant regressive element in his disorder. Day 36.
57. Mrs 12. Evidence to the panel. Day 28.
59. Mrs 2 ran Allergy-induced Autism, a since-disbanded national group.
60. Panel findings of fact. Page 22 (child 4); page 37 (child 8).
61. An academic pharmacist in Sunderland, England, and JABS. “We identified associated gastrointestinal disease and developmental regression in a group of previously normal children, which was generally associated in time with possible environmental triggers.” This claim was retracted by 10 of the 13 authors in March 2004. (Murch SH, Anthony A, Casson DH, Malik M, Berelowitz M, Dhillon AP, et al. Retraction of an interpretation. Lancet2004;363:750.)
66. EMT surgeon. Day 36. “At the age of two years and one month he apparently has a few single words only. He does not seem able to communicate his needs to his mother... Obviously I am more concerned about his increasingly apparent general delay. Mum was asking about this and although initially denying any problem, is obviously concealing quite deep seated worries about him being ‘backward’.”
71. Wheldon Houlbsey. Letter to Neela Shabde. 17 February 1995. Day 29. “I was asked to see [Child 8] last year when there was concern about her development generally. When I saw her in clinic at the age of 10½ months I discovered that she had a coarctation, and referred her to the paediatric cardiologists. This was repaired surgically, and she is now well from this point of view. However concern about her development persists.”
72. For reference, according to Medline Plus, from the US National Library of Medicine and the National Institutes of Health, the typical 18 month old “Can say 10 or more words when asked”. According to the Early Identification of Developmental Delay and Disability project, funded by the state of California, at age 15 months, a child typically “uses 4-6 words”, and at 16-18 months “uses 7-20 words”.
73. Michael Rutter. Evidence to the panel. Day 37. “It is the kind of account that one often gets with an autism spectrum disorder. The fact that the child had only two to three words would make one uncertain as to whether this is a true bill or not, in that that is a very small amount of language to lose, but this is the kind of thing that one often sees so that the picture that comes out of all of these records is of a developmental problem that began early, involves language, involves some autistic-like features, quite
a lot of hyperactivity, so that there does not seem much doubt that there was some sort of pervasive developmental disorder that could be regarded as falling on the autism spectrum at an earlier point."

80. Child 1 was born on 14 January 1993 and received MMR on 19 January 1994.
81. Anthea Barrow. Referral letter. 17 May 1996. "Mr & Mrs 1's most recent concern is that the MMR vaccination given to their son may be responsible for the autism." Day 5.
87. Child 5 was born on 10 December 1988 and received MMR on 10 April 1990.
89. Dr Williams. Letter to Dr Wilkinson. January 1992. Day 11. Day 36. "At one year he had convulsions which led to a further hospital admission but these appear to have been due to a high fever. From then on his parents noticed a difference in his development and feel that these febrile epileptic seizures continue to the present day... At 10 months of age he was saying mummy and daddy but then became very miserable and appeared to lose ground in his development after he had been in hospital."
90. Child 9 was born on 11 June 1990 and received MMR in October 1991.
93. (a) Peter Harvey. Neurology record. 5 December 1996. Day 64. "No doubt about relationship with MMR at onset. No doubt of normal earlier development... Parents have no doubt about the relationship with MMR." (b) David Casson. Discharge summary. 6 December 1996. Day 24. "His parents feel that the onset of his neurodevelopmental symptoms stems from the period two months after having had the MMR vaccination which he received on the 10 April 1990. A few months subsequent to this he started losing his skills." (c) Mohsin Malik. Discharge letter. 14 January 1997. Reported in the first statement of Clifford Spratt. Day 23.
96. The first referral letter for any child in the Lancet series—child 3—was dated 19 February 1996.
97. Andrew Wakefield. Evidence to the panel. Day 66. "Q: What I am suggesting to you and what I now want to ask you is where you make it clear that the children had come to the Royal Free in the first place, at least in the majority of cases, in the letters that we have looked at, because their parents, or in some cases their doctor through their parents, thought that MMR might have caused the damage? A: That is implicit to anyone reading this paper. When we talk in the discussion about a possibility of a referral, selection bias, in a self-referred group, the group is self-referred because of the symptoms manifest by the children, including the history of a possible exposure to a vaccine or an infection that has led to the problem, and then seeking help from a specific unit. That is explicitly what self-referral means. Inherent in that is, to the reader, those elements of the history of the patient that have caused them to come to that unit. To anyone reading this, we would have considered that to be self-evident. Self-referral on the basis of one or more of the symptoms of gastrointestinal problems, developmental regression and an association with environmental exposure... Q: I asked you why you did not make it clear, as we have seen from the letters that we looked at yesterday, that, at least in the vast majority of cases, these children came in the first place because their parents thought that MMR had caused that condition. You immediately to go a line where you talk about self-referral, but that particular reference does not include the very point that I am asking about, and you say is implicit, namely the association with MMR. How does any reader, whether a scientist, doctor or otherwise, read that into what you say there? A: The patients, children, are self-referred based on their symptoms and their history. That contains the three key elements of an environmental exposure, gastrointestinal problems and developmental regression. That self-referral encapsulates those three elements. That is, I would have thought, evident to any reader."
100. Child 3 was born on 3 January 1990 and received MMR on 1 March 1991.
101. Ajegowda Shantha. Evidence to the panel. Day 5. "Q: I think the first record of any parental concern in relation to development was when child 3 was 2½ in June 1992... A: Yes."
was 18 months when this left him. He now has lots of unintelligible babble and appears to understand at one word level.” Day 36.

108. Although, in addition to making a legal claim, they also made a claim to the government’s vaccine damage payments unit, prior to referral. Day 36.


112. Ian Booth. Evidence to the panel. Day 41. “Looking for inflammatory bowel disease would be a most unusual way of approaching a patient with severe, long-standing constipation.”


117. Panel findings of fact. Page 70.


122. Profile: Andrew Wakefield , the man at the centre of the MMR scare. Times2010 May 24. http://www.timesonline.co.uk/tol/news/uk/article7135099.ece

123. Walker-Smith J. Evidence to the panel. Day 97. “We all rely on trust. I trusted Dr Wakefield.”


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**How the vaccine crisis was meant to make money**

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In the second part of a special BMJ series, Brian Deer reveals a secret scheme to raise huge sums from a campaign, launched at a London medical school, that claimed links between MMR, autism, and bowel disease

John Walker-Smith, professor of paediatric gastroenterology, hurried to Malcolm ward on the sixth floor of the Royal Free Hospital, London, with what any doctor would think was bad news. An 8 year old boy, admitted for five days of investigations, had been provisionally diagnosed with Crohn’s disease. But when the child’s mother—here anonymised as “Mrs 2”—years afterwards recounted what happened, she seemed pleased to have received information she expected and made it sound as if Walker Smith was glad too.

“He skipped into that room like a 2 year old,” she told me. She remembered he said: “[Mrs 2], you were right.”

Brightly painted with murals, Malcolm ward was Walker-Smith’s. It came with his employment contract. Exactly one year previously, in September 1995, he had been lured to the Royal Free with many perks, of which this was one. Previously the hospital had no children’s bowel service, but with him it had a chance of the best.

The initiative to recruit him, however, had not come from management. It came from an academic researcher in the gastroenterology department: a former trainee surgeon, Andrew Wakefield.1 He wanted Walker-Smith, who would bring access to children’s gastrointestinal tracts, to help him prove a personal theory. This was that Crohn’s disease was caused by persisting measles virus infections2—most notably, he came to suggest, from vaccines.3

“You used to hear Wakefield’s people talking about how they would win the Nobel Prize for this,” remembers Brent Taylor, the Royal Free’s head of community child health, who frequently clashed with the pair. “The atmosphere here was extraordinary.”
But instead of honours, the two men reaped disgrace. In January and May 2010, the UK’s General Medical Council found them guilty of a raft of charges over a project involving child 2. Wakefield, now 54, was judged by a five member panel to be guilty of some 30 charges, including four counts of dishonesty and 12 of causing children to be subjected to invasive procedures that were clinically unjustified; Walker-Smith, 74, was deemed irresponsible and unethical. Both were struck off the medical register and have since filed High Court appeals.

**Working on a lawsuit**

Their misconduct arose out of a fishing expedition, in which Malcolm ward was the pond for the measles theory. Since February 1996, seven months before child 2’s admission, Wakefield had been engaged by a lawyer named Richard Barr, who hoped to bring a lawsuit against vaccine manufacturers. Barr was a high street solicitor, and an expert in home conveyancing, but also acted for an anti-vaccine group, JABS. And, through this connection, the man nowadays popularly dubbed the “MMR doctor” had found a supply of research patients for Walker-Smith.

“The following are signs to look for,” Barr wrote in a newsletter to his vaccine claim clients, mostly media enlisted parents of children with brain disorders, giving a list of common Crohn’s disease symptoms. “If your child has suffered from all or any of these symptoms could you please contact us, and it may be appropriate to put you in touch with Dr Wakefield.”

The first to be admitted—in July 1996—was a 3 year old boy with autism. But, according to his records, reviewed by the GMC panel, he was so constipated that, despite two attempts, the endoscopist could not reach his small intestine. So child 2, who had diarrhoea (found to be constipation overflow) was the first to have his ileum intubated.

Child 2 also had autism, the first signs of which came on “a few months” after MMR vaccination. His mother was referred to Wakefield by the JABS organiser, and the boy would not only be the lead test case in Barr’s eventual, failed, lawsuit but would feature with 11 other children in a now notorious, retracted, *Lancet* paper linking the vaccine with bowel and brain problems.

He was admitted on Sunday 1 September 1996 and endured a gruelling battery of investigations. These included magnetic resonance imaging of his brain, electroencephalography and evoked potentials, radioactive Schilling test, blood and urine tests, and lumbar puncture—all specified in an agreement with Barr.

**A viral diagnostic**

The following day, Monday, child 2 had an ileocolonoscopy, which, in common with seven other children reported in the paper, the GMC panel would find was not clinically warranted. Tuesday was Wakefield’s 40th birthday. And on Wednesday, with the news that the boy—still on the ward—might have Crohn’s disease, the doctor produced a remarkable document. It was an 11 page draft of a scheme behind the vaccine scare, now revealed for the first time in full.

The document was headed “Investor/school/investor meeting 1.” Based on a patent Wakefield had filed in March 1995 claiming that “Crohn’s disease or ulcerative colitis may be diagnosed by detecting measles virus in bowel tissue, bowel products or body fluids,” it proposed starting a company that could reap huge returns from molecular viral diagnostic tests. It predicted a turnover from Britain and America of up to £72.5m a year.

“In view of the unique services offered by the Company and its technology, particularly for the molecular diagnostic,” the document noted, “the assays can command premium prices.”

To help finance the scheme, Wakefield looked to the government’s legal aid fund—meant to give poorer people access to justice. For the previous seven months, child 2 had been enrolled with Barr’s firm, which since February 1996—two years before the paper’s publication—had been paying the researcher undisclosed fees of £150 an hour, plus expenses.

“The ability of the Company to commercialise its candidate products,” the draft plan continued, “depends upon the extent to which reimbursement for the cost of such products will be available from government health administration authorities, private health providers and, in the context of the molecular diagnostic, the Legal Aid Board.”

As it turned out later, child 2 did not have Crohn’s disease, but three weeks after drafting the plan, Wakefield met three others to discuss it. One was his mentor, Roy Pounder, the Royal Free’s professor of gastroenterology and later vice president of the Royal College of Physicians. The others were Bryan Blatch, the medical school’s secretary, and Cengiz Tarhan, its finance officer.
Money from the lawyer

Discussions about the business continued over the following years, but Wakefield’s involvement with Barr was quickly noted. In October 1996, the medical school’s dean, Arie Zuckerman, a virologist, was told that the lawyer had offered to pay the school for a “clinical and scientific study,” and had sent a first instalment of £25,000. This was held in suspense while Zuckerman sought confidential ethical advice from the British Medical Association, although Wakefield had already started spending it.

“Arising from recent widespread publicity given to this research,” Zuckerman (who told me he does not want to discuss these matters) wrote of Wakefield’s already televised claims about Crohn’s disease, “the Legal Aid Board has provided funding through a firm of solicitors representing Crohn’s disease sufferers and we have been asked to make an appointment to the staff of the Medical School, specifically to undertake a pilot study of selected patients.”

The BMA answered fully the following March, after its ethics committee had considered the issue. It said that money could be accepted provided there was proper research oversight and transparency over funding and patient sources.

But the dean remained concerned and so made an arrangement with the hospital’s chief executive, Martin Else, who managed a charity called the Special Trustees. Else, now chief executive of the Royal College of Physicians (who told me that he was “not aware of any significant issue being raised”), agreed that the charity could take Barr’s payment and hold it as a grant for Wakefield. So the legal money (which eventually totalled £50,000 and seed funded the business scheme) was moved from the medical school into a numbered hospital charity account and then paid out for Wakefield’s research on the MMR vaccine—back in the medical school.

“Further to our conversation regarding the establishment of a fund with the Special Trustees for your income and expenditure associated with the MMR research,” Else wrote to Wakefield, “I can confirm that a grant will be established for the purpose, given your written confirmation that there is no conflict of interest involved.”

Wakefield obliged, but the arrangement raised issues about the two institutions’ involvement in the vaccine crisis. For when the Lancet paper was published, in February 1998, and the scare was launched at a televised press conference, nobody was aware that Wakefield was receiving substantial personal payments from Barr. But both the medical school’s dean and the hospital’s chief executive knew that his research was part funded through a lawyer.

The paper itself, meanwhile, included a funding statement, which Else later told me he did not notice. “This study was supported by the Special Trustees,” it said, with no mention of legal aid or Barr. The lawyer, however, was forthright when later asked. He said he paid for the Lancet research. “I remember noting at the time that the funding acknowledgment wasn’t there,” he told me. “But it didn’t seem to be a big deal, because it just wasn’t a big deal in those days.”

Behind the press conference

Neither school nor hospital stood on the sidelines. They threw their weight behind Wakefield. In the build-up to the press conference, they installed extra phone lines and answering machines to field the expected panic, and distributed to broadcasters a 23 minute video news release showcasing Wakefield’s claims. “There is sufficient anxiety in my own mind for the long term safety of the polyvalent vaccine—that is, the MMR vaccination in combination—that I think it should be suspended in favour of the single vaccines,” he said, in one of four similar formulations on the videotape.

Single vaccine patent filed by Wakefield

The press conference and video boosted the commercial plans, which were moving forward behind the scenes. The following week, Wakefield brought two associates to the school for an already scheduled meeting with the finance officer Tarhan. One was the father of child 10 in the paper. The other was a venture capitalist. And two days after the meeting, they submitted a 13 page proposal to launch a joint business with the school. It would be focused on a new company, Immunospecifics Biotechnologies Ltd, aiming not only to produce a diagnostic test, as proposed 18 months earlier, but also “immunotherapeutics and vaccines.”

Given the previous week’s publicity drive, the vaccine plans were sensitive. But the school had long known of this ambition. First surfacing in Wakefield’s 1995 patent for a diagnostic test for Crohn’s disease, it had been fleshed out in 1997, eight months before the press conference, in a patent for a “safer” single measles shot.

The revised business plan was ambitious and detailed, aiming to raise £2.1m from investors. It spanned the detection of Crohn’s disease, the treatment of autism, and “a replacement for attenuated viral vaccines.”
The methods for the molecular test for Crohn’s disease were newish. But those for the treatment and vaccines were dated. They relied on transfer factor, a largely abandoned fringe technology to move immune cells from person to person. Nevertheless, the school remained interested, and a two year courtship ensued. Even as the vaccine scare escalated, triggering a deluge of referrals to Walker-Smith, staff at Freemedic, the commercial arm of what was now the merged Royal Free and University College Medical School, poured over contracts and plans.

Trading was to be fronted by Carmel Healthcare Ltd—named after Wakefield’s wife. Firmly rooted in Barr’s lawsuit, which eventually paid Wakefield £435 643, plus expenses, the business was to be launched off the back of the vaccine scare, diagnosing a purported—and still unsubstantiated—“new syndrome.” This, Wakefield claimed, comprised both brain and bowel diseases, which, after Crohn’s disease was not found in any of the Lancet children, he dubbed “autistic enterocolitis.”

“It is estimated that the initial market for the diagnostic will be litigation driven testing of patients with AE [autistic enterocolitis] from both the UK and the USA,” said a 35 page “private and confidential” prospectus, which was passed to me by a recipient. It aimed at raising an initial £700 000 from investors and forecast extraordinary revenues. “It is estimated that by year 3, income from this testing could be about £3 300 000 rising to about £28 000 000 as diagnostic testing in support of therapeutic regimes come on stream.”

Carmel was registered in the Irish Republic, where Wakefield would also become a director of another business. This was Unigenetics Ltd, incorporated in February 1999 with a Dublin pathologist, John O’Leary. After Wakefield submitted a confidential report to the Legal Aid Board, Unigenetics was awarded—without checks—£800 000 of taxpayers’ money to perform polymerase chain reaction tests on bowel tissue and blood samples from children passing through Malcolm ward.

The key players in Carmel were the same as in the first company, Immunospecifics, with their planned equity now set out. Wakefield would get 37%, and the father of child 10 22.2%. The venture capitalist would get 18%, Pounder 11.7%, and O’Leary 11.1%. Some would also be awarded extra money in advance, in proposed “executive and non-executive staff costs.” Wakefield was set to get £40 000 a year, in addition to his legal earnings and medical school salary, with an annual travel budget of £50 000 for the business.

Here was another striking conflict of interest, but Wakefield had long made clear his expectations. “The Company will endeavour to ensure that the principal members of its management and scientific team are suitably incentivised by the allocation of Equity and stock options,” he had written in September 1996, when child 2 was still on the ward.

Carmel was to be based at the Coombe Women’s Hospital, Dublin, where legal aid money paid for a laboratory. A prospectus described a public relations effort aimed at two “target” audiences: “parent groups and lawyers representing affected individuals” and “major pharmaceutical companies.”

“Once the work of Professor O’Leary and Dr Wakefield is published, either late in 1999 or early in 2000, which will provide unequivocal evidence for the presence of the vaccine derived measles virus in biopsy samples,” the prospectus said, “the public and political pressure for a thorough, wide ranging investigation into the aetiology of the bowel conditions will be overwhelming.

“As a consequence of the public, political and legal pressures brought to bear, the demand for a diagnostic able to discriminate between wild type and vaccine derived measles strains will be enormous.”

Keeping it secret

To facilitate negotiations, letters and draft contracts went back and forth to the Royal Free. A principal document was finished in the autumn of 1999, naming Wakefield, Pounder, Carmel, Immunospecifics Biotechnologies (IB Ltd), the medical school, Freemedic, an American foundation called Neuro Immuno Therapeutics, and its head, Hugh Fudenberg, an immunologist.

“Royal Free and Immuno entered into the Letter Agreement (as defined in this Agreement),” began a typically meaty clause. “Under its terms Royal Free was to assign to Immuno the intellectual property rights subsisting in the Inventions. In consideration of this assignment Immuno was to pay £10 000 to Royal Free, and was to grant Freemedic an option, over shares representing 10% of Immuno’s issued share capital.”

All of this went forward between the parties in secret. Another document aimed to gag the school. “RFUCMS and Freemedic agree to maintain all information about IB Ltd, its business plan, fund raising proposals etc provided by IB Ltd . . . as confidential and will not disclose the same to any third party and will restrict access thereto to the Directors and senior personnel.”
This latter document was never signed, and strictly therefore of no effect. But University College London (UCL) honoured its spirit, ensuring that the scheme went unreported. And when I was tipped off about Wakefield’s business arrangements, the college fought me for three years under the freedom of information act to keep its involvement hidden.

“UCL is coming to the conclusion,” the college told the hospital in a February 2005 email, “that many of our docs on file fall into the exemption under section 36 of the Act whereby to disclose information ‘would or would be likely to prejudice the free and frank provision of advice; the free and frank exchange of views for the purposes of deliberation or the effective conduct of public affairs.’”

Refusals were authorised by UCL’s provost, Malcolm Grant, a professor of environmental law. Only when Richard Thomas, at the time the UK’s information commissioner, travelled to the college’s offices and later served a formal notice, did they release the documents into my hands.

Among the more striking were those through which the school could deny any involvement in the scheme. “That is to say if Freemedic choose not to be associated with the company in the first instance they may not wish to exercise their options until they are ready to be associated at some time in the future,” Tarhan wrote to child 10’s father in July 1999, as they divided the notional spoils. “We have discussed the reasons for this before.” 40

Another letter—to Wakefield—in November 1999 said: “Therefore neither Freemedic nor the School are in any way involved with Carmel until such options are formally exercised and shares are taken up.” 37

Why investors might have paused
But for all the preparations, ready for presentation to investors, one critical issue for the apparent inventions was not broached—that the company’s ambitious products might not work.

Investment analysts told me that the late 1990s was a prime time to raise cash from optimists. “Money flowing into the City post deregulation had driven the start-up of a load of inexperienced investment schemes in biotech,” one pointed out. “Very few venture capitalists have the technical knowledge.”

Investors might have been encouraged by the mounting vaccine scare and by the Lancet’s backing for Wakefield. 41 But there were curious fundamentals in the secret scheme which the best informed investors might have noticed.

Firstly, transfer factor, for the proposed treatments and vaccines, had long been abandoned by industry. Proposed in the 1940s as a bespoke blood product remedy, it was all but killed by impractical cost, risk of infection, and lack of evidence or standards. Later reformulated as a treated milk pill, as in proposals such as Wakefield’s—which relied on the colostrum of pregnant goats—experts suggest that it is therapeutically inert. 42 Today, it is promoted on the internet as a cure all.

Secondly, there was Hugh Fudenberg, the American immunologist with his Neuro Immuno Therapeutics foundation. He was under sanction at the time from his local medical board over his prescription and use of controlled drugs. 43 When I interviewed him in August 2004 for a Channel 4 documentary, 28 he claimed to cure autism with transfer factor, which he said he rolled out like pizza “three molecules deep” on his North Carolina kitchen table.

“And where does that come from?” I asked.

“From my bone marrow.”

“From your own personal bone marrow?”

“Yeah.”

Another hidden flaw, which would emerge only later, was the Dublin measles tests—over which vaccine lawsuits in Britain and America would founder. 44 These tests were promoted as detecting persistent virus from past MMR vaccinations. But blood from Walker-Smith’s patients, analysed by O’Leary, failed to give consistent results.

For instance, child 2 had all the elements for Wakefield’s theory: regressive autism, bowel problems (actually diagnosed as a food intolerance 45), and a mother who blamed MMR. He was vaccinated at 15 months of age in November 1989. A blood test for the virus 11 years later was negative. Then, two years after that, another result from the boy was positive. Then, two months after that, one was negative.

Preparing for the launch
In advance of such results, Wakefield relied on what he called a series of “impending” papers. “A variety of topics were discussed in the meeting with reference to the forthcoming publication of the paper in Nature (date to be confirmed),” said a confidential Carmel “communications programme,” for example, passed to me by someone present. 46

The launch was scheduled for March 2000, with an attention grabbing stunt three months earlier. No Nature paper appeared, and Wakefield’s platform was to be a London meeting of the Pathological Society
of Great Britain and Ireland. 47 There, with O’Leary and Pounder (who both declined to comment on my findings), he planned to present research claiming a breakthrough. Based on alleged gut biopsy samples from Walker-Smith’s patients—10 with autism and three with Crohn’s disease—tested at the Dublin laboratory, it claimed a “possible causal link” and, given a Wakefield presentation, promised a storm like the press conference two years before.

Meanwhile, he nurtured relationships, with drug industry support, including front of the plane overseas travel. “Please find enclosed a cheque for £2876.70 from Axcan Pharma Inc, a refund of my airfare with regard to my Canadian trip,” 48 he told the special trustees, for example, as he put final touches to the scheme. He was also then negotiating a Johnson & Johnson consultancy 49 and had longstanding connections with Merck and SmithKline Beecham.

The scheme unravels
But as the Carmel plans were finalised, Wakefield’s fortunes reversed. On the brink of his business launch, it founndered.

The unravelling began after the arrival in the school of a new head of medicine: Mark Pepys. A fellow of the Royal Society and a specialist in amyloid diseases, he brought huge grants and was now the school’s biggest name. He was astounded to find Wakefield being feted. “I said I wouldn’t transfer my unit if he was there,” Pepys told me. “And you know what they did? They promoted him.”

With Chris Llewellyn-Smith, a theoretical physicist and at that time UCL’s provost, Pepys struck in December 1999, barely two months after starting at the Royal Free. Wakefield was summoned from the hospital’s Hampstead campus to the college’s central London headquarters. He was challenged over the scheme, then on the verge of fruition, and was given a two page letter.

“We remain concerned about a possible serious conflict of interest between your academic employment by UCL, and your involvement with Carmel,” it said, in part. “This concern arose originally because the company’s business plan appears to depend on premature, scientifically unjustified publication of results, which do not conform to the rigorous academic and scientific standards that are generally expected.” 50

This marked the end of any commercial deals with Wakefield, and the beginning of his end at the Royal Free. When eventually ousted from his job, he said, “I have been asked to go because my research results are unpopular.” 51 And in response to my investigation, he would allege sinister conspiracies to stop him revealing what he claimed were vaccine secrets. 52 53

But the paperwork does not show this. Despite all that had happened, UCL volunteered to support his work. It offered him continuation on the staff, or a year’s paid absence, to test his MMR theories. He was promised help for a study of 150 children (to try to replicate his Lancet claims from just 12) and, in return for withdrawing from the January London conference, he would be given the intellectual property free.

“Good scientific practice,” the provost’s letter stressed, “now demands that you and others seek to confirm or refute robustly, reliably, and above all reproducibly, the possible causal relationships between MMR vaccination and autism/autistic enterocolitis/inflammatory bowel disease that you have postulated.”

At the time, Wakefield agreed. Then his employer waited. It prompted, waited longer, and prompted again. “Three months have elapsed,” Llewellyn-Smith wrote to him in March 2000, asking for “a progress report on the study proposed” and “not to make any public statements” in the meantime. 54

But the study did not happen. The 1998 Lancet research had been a sham. 10 Trying to replicate it with greater numbers would have been hopeless.

Wakefield, however, shrugged off his non-compliance as arising from some fault of the school’s. “It is clear that academic freedom is essential, and cannot be traded,” he eventually responded in September 2000. “It is the unanimous decision of my collaborators and co-workers that it is only appropriate that we define our research objectives, we enact the studies as appropriately reviewed and approved, and we decide as and when we deem the work suitable for submission for peer review.” 55

This was a step too far, and in October 2001 Wakefield was shown the door. As I understand it, he got two years’ money, a statement clearing him of misconduct, the intellectual property for £10, uncollected, and a gag on Royal Free comment. “We paid him to go away,” Pepys told me. “And, of course, one of the conditions of him going away was that I wasn’t supposed to say anything critical of him to anybody, for ever after.”

Wakefield would never perform the research anywhere, or prove his measles theory. His vaccine plans—predictably—went nowhere. And when I put these matters to him, he and his lawyers acknowledged receipt but offered no further response.
Public fears over the vaccine had yet to reach their peak. My investigation would not begin for two years. But Wakefield would never again hold an academic post, and the secret scheme behind the scare was no more.

Footnotes

• Funding: Brian Deer’s investigation was funded by the Sunday Times of London and the Channel 4 television network. Reports by Deer in the BMJ were commissioned and paid for by the journal. No other funding was received, apart from legal costs paid to Deer by the Medical Protection Society on behalf of Andrew Wakefield.

• Competing interests: The author has completed the unified competing interest form at www.icmje.org/coi_disclosure.pdf (available from him on request) and declares no financial relationships with any organisation that might have an interest in this work; BD’s investigation led to the GMC proceedings referred to in this report, including the charges. He made many submissions of information, but was not a party or witness in the case, nor involved in its conduct.

• Provenance and peer review: Commissioned; not externally peer reviewed.

References

7. MMR and MR Vaccine Litigation Sayers and others v Smithkline Beecham plc and others—[2007] All ER (D) 30 (Jun).
9. www.timesonline.co.uk/tol/news/uk/article1265373.ece
13. Although Wakefield and the Lancet would later claim that the Legal Aid Board commissioned a quite separate “viral” study, the work specified in the documents submitted to the Legal Aid Board, seeking funding, on 6 June 1996, included clinical examination, ileocolonoscopy, histology, immunohistochemistry and molecular analysis for measles virus, neuropsychiatric studies, MRI brain scan, lumbar puncture, EEG and evoked potentials, B12 studies, modified Schilling test, and various blood and urine tests. The document includes costings, such as £1,750 for colonoscopy with four night’s stay, £1,000 for MRI scans, and £1,400 for medical reports. Molecular, immunohistochemical and electron microscopic analysis of tissues was priced at £500 per child. Named investigators for the legal project who would also be authors of the Lancet paper were Andrew Wakefield, John Walker-Smith, Simon Murch, David Casson, Amar Dhillon, John Linnell, Mark Berelowitz and Peter Harvey. The document states: “The objective is to seek evidence which will be acceptable in a court of law of the causative connection between either the mumps, measles and rubella vaccine or the measles/rubella vaccine and certain conditions which have been reported with considerable frequency by families of children who are seeking compensation. It is hoped that using the testing protocol attached it will be possible to establish the causal link between the administration of the vaccines and the conditions outlined in this proposed protocol and costing proposal.” The board commissioned the project under an “authority to do contract work”, naming Wakefield, issued on 22 August 1996. The technical specification is materially identical to a protocol submitted for approval by the Royal Free’s ethics committee, and work to be performed materially
identical to the study submitted by Wakefield to the Lancet, with data sliced into two paired papers, which were peer-reviewed together. One was published on 28 February 1998, and the other was rejected by the journal.

41. Peter Lachman. Evidence to the panel. Day 47. “In general I would imagine it is very much like drinking goat’s milk; I would not imagine it was any more dangerous than that...The more probable is that it would have no particular effects at all.”
45. Carmel Healthcare. Outline PR plan and action list ahead of Andrew Wakefield’s presentation at the Pathological Society of Britain & Ireland on 17/01/00 [sic].

High prevalence of asymptomatic cardiac abnormalities in patients with HIV
Michael Carter
Published: 10 January 2011
Asymptomatic cardiac abnormalities are common among HIV-positive patients, US investigators report in the online edition of Clinical Infectious Diseases.

Much higher than expected rates of structural and functional cardiac abnormalities were detected when a large number of patients were monitored using echocardiographs.

“Cardiac abnormalities were commonly detected by echocardiography, despite the relatively young age and high CD4 cell counts of the participants,” comment the investigators.

However, many of the risk factors associated with the cardiac abnormalities were potentially modifiable.

Thanks to the effectiveness of antiretroviral therapy many patients with HIV can expect to live well into older age.

But there is concern that some individuals have an increased risk of cardiovascular disease. Research suggests that patients with HIV are more likely to have a heart attack or stroke than their HIV-negative peers. The causes of this increased cardiovascular risk seem to include HIV itself, therapy with some antiretroviral drugs and traditional factors such age, smoking and diet.
Prevention of cardiovascular disease is an increasingly important component of HIV care. As many of the risks are potentially modifiable, early detection of problems means that patients can be encouraged and supported to make lifestyle changes that reduce their risk of experiencing a cardiac event.

However, little is known about the prevalence and risk factors of asymptomatic structural and functional cardiac dysfunction. Therefore investigators from the US Study to Understand the Natural History of HIV/AIDS in the ERA of Effective Therapy (SUN Study) monitored 656 patients for these abnormalities using echocardiography.

The research was conducted between 2004 and 2006. The patients had a median age of 41 years. Most (76%) were men, 71% were white, and 73% were taking antiretroviral drugs. The patients had well preserved immune function and their median CD4 cell count was 462 cells/mm$^3$. Nearly all (91%) of the individuals who were receiving antiretroviral therapy had a viral load below 400 copies/ml.

Only a third of patients were found to have normal cardiac function and structure.

Results showed that 18% of individuals had left ventricular systolic dysfunction; 26% had diastolic dysfunction; 57% pulmonary hypertension; left ventricular hypertrophy was present in 7% of individuals, and left arterial enlargement in 40%.

The investigators note that these prevalences are much higher than those seen in the general US population. For example, in one recent study only 5% of HIV-negative patients had an enlarged left artery.

Statistical analysis showed that a range of risk factors were associated with the abnormalities observed in the HIV-positive patients.

Those for left ventricular systolic dysfunction included a history of heart attack (p = 0.019), high levels of a marker of inflammation, C-reactive protein (p = 0.033), and smoking (p = 0.036).

Diastolic dysfunction was also associated with high levels of C-reactive protein (p = 0.027) and high blood pressure (p = 0.003).

Risk factors for pulmonary hypertension included current use of the protease inhibitor ritonavir (p = 0.037).

The investigators identified high blood pressure (p = 0.002), diabetes (p = 0.003), black race (p = 0.006), elevated C-reactive protein (p = 0.15) and current treatment with abacavir (p = 0.02) as risk factors for left ventricular hypertrophy. Women with a body mass index above 25 also had an increased risk of this abnormality.

Only two factors were associated with left arterial enlargement: high blood pressure (p = 0.008) and recent use of cannabis (p = 0.013).

None of these risk factors were “unexpected” comment the investigators, and they stress that many are potentially modifiable.

They therefore conclude, “our results support lifestyle modifications, such as smoking cessation and weight loss, as continued priorities in the chronic management of HIV infection.”

Reference

Engineering team invents lab-on-a-chip for fast, inexpensive blood tests
Next step will turn blood testing into a smartphone application
KINGSTON, R.I. – January 10, 2011—While most blood tests require shipping a vial of blood to a laboratory for analysis and waiting several days for the results, a new device invented by a team of engineers and students at the University of Rhode Island uses just a pinprick of blood in a portable device that provides results in less than 30 minutes.

"This development is a big step in point-of-care diagnostics, where testing can be performed in a clinic, in a doctor’s office, or right at home," said Mohammad Faghri, URI professor of mechanical engineering and the lead researcher on the project. "No longer will patients have to wait anxiously for several days for their test results. They can have their blood tested when they walk into the doctor’s office and the results will be ready before they leave."

With the new lab-on-a-chip technology, a drop of blood is placed on a plastic polymer cartridge smaller than a credit card and inserted into a shoebox-sized biosensor containing a miniature spectrometer and piezoelectric micro-pump. The blood travels through the cartridge in tiny channels 500 microns wide to a detection site where it reacts with preloaded reagents enabling the sensor to detect certain biomarkers of disease.

Several patents are pending on the invention.
Compared to similar devices in development elsewhere, the URI system is much smaller, more portable, requires a smaller blood sample, and is less expensive. While the sensor costs about $3,200, each test costs just $1.50, which is the cost for the plastic cartridge and reagents.

The first cartridges the researchers developed focus on the detection of C-reactive proteins (CRP) in the blood, a preferred method for helping doctors assess the risk of cardiovascular and peripheral vascular diseases. From 2002 to 2004 (the only years for which data are available), the number of CRP tests paid for by Medicare tripled from 145,000 to 454,000, and it is estimated that those numbers have quadrupled since then.

Faghri said that additional cartridges can be designed to detect biomarkers of other diseases. The researchers are already working to engineer the device to detect levels of the beta amyloid protein that can be used as a predictor of Alzheimer's disease. The device can also be engineered to detect virulent pathogens, including HIV, hepatitis B and H1N1 (swine) flu.

The next generation of the device will incorporate a hand-held sensor that will reduce manufacturing costs. Faghri also envisions a further miniaturization of the invention that can be adapted as a smartphone application. By embedding the biosensor in the cartridge and using the computer power of the phone, as well as its wireless communication capabilities, Faghri believes that patients may be able to conduct the tests themselves and have the results transmitted immediately to their doctor's office via their phone. Among many other benefits, this should help to significantly reduce health care costs.

"We are already making progress on many of the steps toward the next generation of the system, and it won't be long before we can begin to commercialize it," Faghri said.

**Warning Over Cancer Explosion as More Resort to ARV Therapy**

**Bernard James**

8 January 2011

Dar es Salaam — While Tanzania has commendably raised the number of patients on life-prolonging anti-retroviral drugs (ARVs), doctors are, however, now grappling with how to deal with a cancer burden among those using the life-prolonging medication.

Medical experts say there is an evident rise in cases of Aids-related types of cancer as more and more people turn to ARVs for survival. The danger, is that the local health system was not prepared enough to deal with an emerging trend in cancer infections as fewer people living with HIV/Aids die from the disease due to the therapy.

Cancer experts have warned therefore that the nation should get prepared to tackle a cancer pandemic to increase further in the near future with many Aids patients taking the life-prolonging drugs.

According to Dr Diwani Msemo, before the advancement of life-prolonging drugs, patients succumbed early but with the improvement of Aids treatment, many now live much longer.

Dr Msemo, who is a senior expert with the Ocean Road Cancer Institute (ORCI), said unlike in the past, cancer and HIV/Aids are now considered chronic and would require plans to accommodate a bigger number of patients. The ORCI is Tanzania's only specialized centre for treatment of cancer.

"As chances for developing cancer for the people on ARV drugs has increased, we are likely to see an eruption of cases of Aids related cancer in the years to come than we see now," he said in an interview with The Citizen. Types of Aids-related cancer include Kaposi's sarcoma, defused B cell lymphoma, cancer of conjunctiva (eye cancer), "aggressive" cancer of the cervix and anus.

"So, as we are now tackling Aids using ARVs, we should be prepared to tackle cancer which will be developing among HIV/Aids survivors," said Dr Msemo who added that the number of other types of cancer related to HIV is also on the increase.

He said statistics over the 30 years of HIV pandemic indicate that the number of patients with Kaposi's sarcoma (skin and blood vessels) has increased from 1 per cent in 1990 to 15 per cent 2010. Interestingly, more than 95 per cent of them are infected with HIV.

"In 1990 we used to see some 400 to 500 cancer patients here at ORCI. Out of those, only one to two per cent had Kaposi's sarcoma but as at last year this percentage was 15 per cent," said Dr Msemo. Kaposi's sarcoma is the second commonest type of cancer affecting the Tanzania population after cervical cancer whose prevalence is at 40 per cent. In total, ORCI currently sees almost 4,000 new cancer patients every year.

Scientists have established that people with suppressed/defective immunity due to HIV/Aids are more likely to develop these types of cancers. The World Health Organisation (WHO) estimates for 2000
show that 21,000 new cancer cases occur each year in Tanzania. Some 10,000 patients die of cancer in the country over the same period.

The story of HIV/AIDS-related cancer does not end with Kaposi’s sarcoma. Scientists have in 1985 found that majority of patients with Burkitt’s lymphoma also are HIV-positive.

Although there are still some disagreement, cancer experts had in 1993 also found that people with HIV, were likely to get "aggressive cervical cancer", Dr Msemo cautions that not that everybody with cervical cancer is HIV-positive.

"This is to say if you have cervical cancer and you have HIV, your cancer of cervix is likely to progress fast than someone without Aids." Another type of cancer, which is apparently associated with HIV is the cancer of the conjunctiva, or eye cancer.

The Permanent Secretary in the ministry of Health and Social Welfare, Ms Blandina Nyoni, told The Citizen on Saturday over the phone yesterday that the government, being aware of the looming problem, was directing most of its effort to the source of the scourge by enhancing HIV prevention strategies.

"Our major drive is to make people avoid getting new infections and for the infected, ensure they access treatment," the PS said.

**Inovio Pharma’s Novel DNA Vaccine For Clade C HIV Achieves Immune Responses**

1/10/2011  
(RTTNews)—Inovio Pharmaceuticals, Inc. (INO:News ) Monday announced the publication of a scientific paper highlighting positive preclinical results from Inovio’s novel DNA vaccine targeting HIV Clade C viruses in the journal Vaccine.

Clade C is the predominant HIV-1 strain infecting people in sub-Saharan Africa, India, and China, and there is a critical need for a vaccine targeted to these areas.

In the study, the vaccine induced strong antibody and T-cell immune responses in rhesus monkeys. The vaccinated monkeys showed protective effects against a subsequent challenge with an infectious dose of SHIV virus compared to the placebo control animals. These results further support the proof of concept for Inovio’s global DNA vaccine candidates, PENNVAX-G and PENNVAX-GP in a relevant preclinical model.

**Immune paradox**

Why is it that some HIV patients treated with antiretrovirals end up suffering from a new immunopathology? Martyn French is trying to solve this puzzling conundrum.

Almost as long as HIV patients have been receiving antiretroviral therapy (ART) to suppress their viral load and correct the associated immunodeficiency, clinicians have been noticing something a bit strange: in some patients, the restored immune response leads to new immunopathology that arises despite control of the infection. It seems that in these individuals, the immune system itself is causing new problems.

This aspect of immune recovery in HIV patients, called immune restoration disease (IRD) has been the main focus of Professor Martyn French’s research for over a decade at the Royal Perth Hospital and University of Western Australia.

“We actually first described this phenomenon in Perth some years ago and it is now recognised as a major problem throughout the world in HIV sufferers from resource-poor countries who are starting ART,” he says.

The disease is usually encountered in people who are very immune-deficient when they start the therapy and who are co-infected with an opportunistic pathogen. Between 10 and 40 per cent of such patients show a pathogen-specific immune response that may cause severe disease.

Tuberculosis (TB) due to infection with *Mycobacterium tuberculosis* is the most common cause of IRD in HIV-infected patients during the initial months of ART, with other common pathogens including *Cryptococcus*, herpes viruses, and hepatitis B and C virus.

“For example, in South Africa it is very common for people to present with HIV and TB, and people treated for both can develop a condition that is commonly referred to as TB-associated immune reconstitution inflammatory syndrome [TB-IRIS],” says French.

“This is basically a form of IRD where the disease is actually caused by the immune system recovering, rather than by immunodeficiency. It seems that the body’s fight to clear the mycobacterial infection in the presence of an ART-driven immune recovery leads to an exaggerated inflammatory response that itself causes quite serious illness.”
At the Australasian Society for Immunology Scientific Meeting held in Perth in December, French will talk about this mechanistic phenomenon that occurs when mycobacteria interact with the immune system during ART.

He will also highlight that this TB disease can take two forms: one where you unmask an undiagnosed case of TB with the ART treatment; and the other when you seem to cause a paradoxical relapse of recently treated TB.

His discussions will be based largely on results from a major study that French’s group contributed to in Cambodia looking at the immunopathogenesis of TB-IRIS. This was done in collaboration with scientists in Melbourne, Sydney and Phnom Penh and funded by AusAID and the NHMRC.

The Cambodian findings essentially showed that IRD associated with *M. tuberculosis* infection involves both T cell responses to mycobacterial antigens and responses by the innate immune system.

“It seems that those HIV patients with treated TB who develop TB-IRIS on ART show innate responses in addition to the expected T cell response,” says French.

“There was also a group of patients that presented with TB after starting ART, in whom the immune response induced by ART was a really strong T cell response to the mycobacterial antigens. So in the patients where you unmask the TB, the T cell response seems to dominate, whereas in those where there seems to be a paradoxical relapse of the TB [already treated before ART], the innate responses predominated.”

In answer to the obvious question, French’s team has no idea yet as to why this is. Some recent evidence indicates that it may be related to the severity of the prevailing immune deficiency prior to the HIV therapy, so the immune system in people with very high pathogen loads launches this massive all-out attack against the TB antigens when suddenly boosted by the ART. This leads to a hyper-inflammatory response to the infection.

Around the world this type of abnormal immune response to treated TB is known as paradoxical TB-IRIS, because instead of getting better, paradoxically, the infection seems to get worse. According to French, the terminology comes from the old TB literature, well before HIV, when TB physicians noticed that some TB patients actually got worse when treated.

Nobody understood what was causing that either, and it quite possibly reflects a similar mechanism – with dead and dying bacteria from the TB treatment inducing a hyper-inflammatory reaction. French notes that “in the HIV patients it is probably far worse, because on top of that you are restoring the immune system by treating the HIV.”

About 20 per cent of people with HIV and TB will develop this complication and careful patient management is needed to minimise the severity and symptoms of the inflammation. Work on prevention and treatment strategies for IRD continues worldwide and recent studies also indicate some beneficial effects from steroid administration in severe cases.

This is encouraging because while death rates are not so high with TB-IRIS as long as the morbidity is controlled, ART-treated HIV patients presenting with *Cryptococcus*, the second most common pathogen associated with IRD in HIV patients, fare much worse. More than one-third of these patients are likely to die due to severe meningitis, highlighting why IRD has become so important worldwide as an HIV-related issue.

“In resource-poor countries with high levels of HIV infection, the ART was often stopped because the effect was mistakenly thought to be toxicity from the drugs, when in fact it is a beneficial effect of the ART, but just one that is undesirable. The recommended approach now is to continue the ART and manage the inflammation.”

French and his colleagues Professor Patricia Price, Dr Sonia Fernandez, Dr Andrew Lim and Dr Silvia Lee, who have also worked on the immunology of HIV and HCV infection for many years, hope to understand the mechanistic nature of the immune responses being activated by ART in the presence of different pathogens and eventually find new ways to tame the hyper-inflammatory response.

Learning more about the immune activation going on in these co-infected patients could also provide novel insights about HIV disease itself and, ultimately, how to develop new treatments for this ever-challenging virus infection.

**Pandemic flu strain could point way to universal vaccine**

The search for a universal flu vaccine has received a boost from a surprising source: the 2009 H1N1 pandemic flu strain.
Several patients infected with the 2009 H1N1 strain developed antibodies that are protective against a variety of flu strains, scientists from Emory University School of Medicine and the University of Chicago have found. The results were published online Monday in the *Journal of Experimental Medicine*.

"Our data shows that infection with the 2009 pandemic influenza strain could induce broadly protective antibodies that are only rarely seen after seasonal flu infections or flu shots," says first author Jens Wrammert, PhD, assistant professor of microbiology and immunology at Emory University School of Medicine and the Emory Vaccine Center.

"These findings show that these types of antibodies can be induced in humans, if the immune system has the right stimulation, and suggest that a pan-influenza vaccine might be feasible."

The antibodies isolated from a group of patients who were infected with the 2009 H1N1 strain could guide researchers in efforts to design a vaccine that gives people long-lasting protection against a wide spectrum of flu viruses, say the researchers. Next, the research team is planning to examine the immune responses of people who were vaccinated against the 2009 H1N1 strain but did not get sick.

The research comes from a collaboration between the laboratories of Rafi Ahmed, PhD, at Emory and Patrick Wilson, PhD at the University of Chicago. Ahmed is director of the Emory Vaccine Center and a Georgia Research Alliance Eminent Scholar. Wilson is assistant professor of medicine at the University of Chicago’s Knapp Center for Lupus and Immunology Research.

Scientists from Columbia, Harvard and the National Institutes of Health (NIH) also contributed to the study, which was funded by the National Institute of Allergy and Infectious Diseases, part of the NIH, and by the American Recovery and Reinvestment Act of 2009.

The nine patients studied were recruited through the Hope Clinic, the clinical division of the Emory Vaccine Center. They had a range of disease severities, from mild illness that waned after a few days to a severe case that required a two-month hospital stay including ventilator support. Most of the participants were in their 20s or 30s. Blood samples were usually taken about 10 days after the onset of symptoms.

The team of researchers identified white blood cells from the patients that made antibodies against flu virus, and then isolated the antibody genes from individual cells. They used the genes to produce antibodies in cell culture—a total of 86 varieties—and then tested which flu strains they reacted against.

Five antibodies isolated by the team could bind all the seasonal H1N1 flu strains from the last decade, the devastating "Spanish flu" strain from 1918 and also a pathogenic H5N1 avian flu strain.

Seasonal flu shots contain three inactivated viral strains, each grown in chicken eggs. Over the last decade, it was standard that one of the three is an H1N1 strain. However, vaccination with any one H1N1 strain doesn't usually result in protection against all of them – that's why the 2009 strain could make so many people sick.

Some of the antibodies the team identified stick to the "stalk" region of part of the virus (a protein called hemagglutinin). Because this part of the virus doesn't change as much as other regions, scientists have proposed to make it the basis of a vaccine that could provide broader protection.

"Previously, this type of broadly protective, stalk-reactive antibody was thought to be very rare," Wrammert says. "In contrast, in the patients we studied, these stalk-reactive antibodies were surprisingly abundant."

The team tested whether three of the antibodies they isolated could protect mice against the 2009 H1N1 strain or two other common lab strains. Two antibodies could protect mice against an otherwise lethal dose of any of the three strains, even when the antibody was given 60 hours after infection. However, one antibody only protected against the 2009 H1N1 strain.

The antibody that only reacted to the 2009 H1N1 strain came from the patient with the most severe illness. The antibody genes from that patient suggest that the patient had a complete lack of preexisting immunity to H1N1 viruses, the authors write. In cases where patients experienced a milder illness, it appears that immune cells that developed in response to previous seasonal flu shots or infections formed a foundation of response to 2009 strain.

"The result is something like the Holy Grail for flu-vaccine research," says study author Patrick Wilson, PhD, assistant professor of medicine at the University of Chicago. "It demonstrates how to make a single vaccine that could potentially provide permanent immunity to all influenza. The surprise was that such a very different influenza strain, as opposed to the most common strains, could lead us to something so widely applicable."
Heterosexual Anal Sex Experiences Among Puerto Rican and Black Young Adults

Perspectives on Sexual & Reproductive Health Vol. 42; No. 4: doi:10.1363 (12..2010) Marion Carter; Dare HenrykMoss; Linda Hock-Long; Anna Bergdall; Karen Andes

The authors introduced the study by noting that heterosexual anal sex, which poses risks for STDs, “is not uncommon in the United States.” “However, who engages in it and why are not well understood, particularly among young adults.”

In Hartford, Conn., and Philadelphia from 2006 to 2008, data on topics related to sexual health were collected via survey (483 respondents) and qualitative interviews (70 individuals) from black and Puerto Rican persons ages 18 to 25. Predictors of anal sex with the most recent serious heterosexual partner were assessed by bivariate and multivariate analyses. The team analyzed interview transcripts to assess experiences with anal sex and reasons for engaging or abstaining.

Anal sex was reported by 34 percent of survey respondents. It was more common with serious (22 percent) as opposed to casual (8 percent) partners. Black participants were less likely than Puerto Rican respondents to report anal sex (odds ratio, 0.3); women were more likely than men to report anal sex (2.9).

The qualitative cohort found perceptions of anal sex as painful and unappealing were the predominant reasons for abstaining. Sexual pleasure and, in serious relationships, intimacy were the main reasons cited for engaging in it. During anal sex, condom use “was rare and was motivated by STD or hygiene concerns.”

“Heterosexual anal sex is not an infrequent behavior and should be considered in a broad sexual health context, not simply as an indicator of STD risk,” the authors concluded. “Health providers should address it openly and, when appropriate, as a positive sexual and emotional experience.”

Herpes Virus' Tactical Maneuver Visualized in 3-D

ScienceDaily (Jan. 10, 2011) — For the first time, researchers have developed a 3-D picture of a herpes virus protein interacting with a key part of the human cellular machinery, enhancing our understanding of how it hijacks human cells to spread infection and opening up new possibilities for stepping in to prevent or treat infection. This discovery uncovers one of the many tactical manoeuvres employed by the virus.

The Biotechnology and Biological Sciences Research Council (BBSRC)-funded team, led by The University of Manchester, have used NMR—a technique related to the one used in MRI body scanners and capable of visualizing molecules at the smallest scales—to produce images of a herpes virus protein interacting with a mouse cellular protein. These images were then used to develop a 3-D model of this herpes virus protein interacting with human protein. The research is published in PLoS Pathogens.

Lead researcher Dr. Alexander Golovanov from Manchester’s Interdisciplinary Biocentre and Faculty of Life Sciences said: "There are quite a few types of herpes viruses that cause problems as mild as cold sores through to some quite serious illnesses, such as shingles or even cancer. Viruses cannot survive or replicate on their own—they need the resources and apparatus within a human cell to do so. To prevent or treat diseases caused by viruses we need to know as much as possible about how they do this so that we can spot weak points or take out key tactical manoeuvres."

The 3-D model shows how the viral protein piggybacks onto the molecular machinery components inside human cells, promoting virus replication and spread of infection through the body.

"When you look at the image, it’s like a backpack on an elephant: the small compact fragment of viral protein fits nicely on the back of the human protein," said Dr. Golovanov.
By studying the images along with biochemical experiments using the human version of the cellular protein, the team has uncovered the mechanism by which the viral and cellular proteins work together to guide the viral genetic material out of the cell’s nucleus. Once there, the genetic material can be utilized to make proteins that are used as building blocks for new viruses. The researchers have also confirmed that this relationship between the two proteins exists for related herpes viruses that infect monkeys.

Dr. Golovanov continued: "Our discovery gives us a whole step more detail on how herpes viruses use the human cell to survive and replicate. This opens up the possibilities for asking new questions about how to prevent or treat the diseases they cause."

Professor Janet Allen, BBSRC Director of Research said: "This new research gives us an important piece of the jigsaw for how a particular viral infection works on a molecular level, which is great news. Understanding the relationship between a human, animal or plant—the host—and the organisms that cause disease—pathogens—is a fundamental step toward successful strategies to minimize the impact of infection. To study host-pathogen relationships we have to look in detail at the smallest scale of molecules—as this study does—and also right through to the largest scale of how diseases work in whole systems—a crop disease in the context of a whole area of agricultural land, for example. BBSRC's broad portfolio of research into host-pathogen relationships facilitates this well."

Journal Reference:

Shingles vaccine associated with 55 percent reduced risk of disease
Kaiser Permanente research strengthens national recommendations

PASADENA, Calif. (January 11, 2011) — Receiving the herpes zoster vaccine was associated with a 55 percent reduced risk of developing shingles, according to a Kaiser Permanente study of 300,000 people that appears in the current issue of the Journal of the American Medical Association.

This retrospective study observed the outcomes of the effectiveness of the herpes zoster vaccine in a large, diverse population of men and women ages 60 years and older. Researchers found a significant reduced risk of shingles across all sub-groups—those who are healthy as well as those with chronic conditions including diabetes or heart, lung or kidney diseases.

These study findings differ from the clinical trial of the vaccine, which observed its effectiveness on 38,000 participants 60 years of age and older and found it less effective for people older than 75. This new study found a 55 percent reduced risk of shingles among both adults 60 years and older, as well as adults 75 years and older who received the vaccine.

These findings support Centers for Disease Control and Prevention recommendations to offer the vaccine to eligible patients of all ages, including those over 75. Researchers note that additional examination of the vaccine’s effect in the oldest group should continue. The herpes zoster vaccine was licensed in 2006, but uptake in the United States remains low: about 10 percent in 2009 in adults 60 years and older.

“Our study shows the vaccine has the potential to prevent tens of thousands of cases of shingles, a painful, lingering disease,” said study lead author Hung Fu Tseng, PhD, MPH, a research scientist with the Kaiser Permanente Department of Research & Evaluation in Pasadena, Calif. "We suggest clinicians follow the CDC’s recommendations to talk to their patients about the option of vaccination against this serious condition."

There are more than 1 million episodes of shingles every year in the United States. Shingles is a painful condition that can last months or years and can seriously impact quality of life. Shingles is caused by the dormant chickenpox virus, which stays in the body after a person has recovered from chickenpox. The virus can reactivate and replicate and cause shingles and damage to the nerve system. The elderly are especially vulnerable because as we age, our immunity against the virus that causes shingles declines.

“The risk of developing shingles during a lifetime is about 30 percent. It is therefore reassuring to confirm results of the original clinical trial that herpes zoster vaccine is effective at preventing this painful disease,” said study co-author Rafael Harpaz, MD, MPH, an epidemiologist with the Centers for Disease Control and Prevention’s National Center for Immunization and Respiratory Diseases. “Although that trial was well done, one cannot be sure a vaccine works outside a research setting until you evaluate it in routine medical practices. In addition, our study also provided new information that the vaccine worked to prevent shingles involving the eye, which can result in very serious complications.”
Researchers conducted a retrospective observational study that looked at 75,761 vaccinated and 227,283 unvaccinated male and female members of Kaiser Permanente in Southern California from 2007 to 2009, using electronic health records to compare the incidence of shingles of the vaccinated and unvaccinated populations. Results remained after taking into account differences in sex, race, chronic diseases, and prior utilization.

This is the latest in a series of published Kaiser Permanente studies undertaken to better understand vaccine effectiveness and safety. Dr. Tseng published another study in JAMA that found the pneumococcal pneumonia vaccination is not associated with a reduced risk of heart attacks or strokes. Another Kaiser Permanente study found the combination vaccine for measles, mumps, rubella and chickenpox (MMRV) is associated with double the risk of febrile seizures for 1- to 2-year-old children compared to same-day administration of the separate vaccine for MMR (measles, mumps, rubella) and the varicella (V) vaccine for chickenpox. Other recent published Kaiser Permanente studies found children of parents who refuse vaccines are nine times more likely to get chickenpox and 23 times more likely to get whooping cough compared to fully immunized children. A study published last year found that herpes zoster, also known as shingles, is very rare among children who have been vaccinated against chickenpox.

**Couples Navigate Love and HIV**


The number of HIV serodiscordant couples in the United States is growing. While these relationships underscore the power of love over fear, they also bear witness to the challenges of living with HIV, even three decades into the AIDS epidemic.

“I know more and more people who are choosing HIV-infected partners,” said Lora Branch, former director of the STD/HIV division at the Chicago Department of Public Health. “It’s not that unusual anymore.”

Though it is not known how many HIV-positive people are in serodiscordant couples, a 2001 study in the journal Family Planning Perspectives offered some insight. It found that half the HIV-positive men and women surveyed about their desire to have children said their spouse was HIV-negative, according to Dr. Deborah Cohan, associate professor of obstetrics, gynecology, and reproductive sciences at the University of California-San Francisco.

Branch believes same-sex and opposite-sex couples comprise equal numbers of serodiscordant relationships, which span the range of racial and class categories.

Knowing when to disclose one’s HIV status to a prospective partner can be difficult, said Celeste Watkins-Hayes, an HIV/AIDS researcher and faculty fellow at the Institute for Policy Research at Northwestern University. In some circumstances, a person enters a relationship not knowing their partner is infected, either because the information is not disclosed right away or it is not yet known. The eventual disclosure can be an emotional rollercoaster.

“For many people it is a difficult relationship because it comes with guilt on the infected person’s part. There is always this layer of stigma and shame, which is very real in this country, particularly in the black community,” said longtime Chicago HIV/AIDS activist Rae Lewis-Thornton. “That is a barrier that must be overcome before couples get to a really good place and can be comfortable.”

**Rise in Abortions in China, Young Women Targeted**

*Associated Press*, (01.09.2011) Alexa Olesen

Abortion clinics in China are seeing a very different clientele than they did in the early years of the government’s one-child-per-couple rule, providers say. Younger, unmarried women now comprise many, if not most, of those seeking abortions. Many experts cite the burgeoning openness toward premarital sex and a lack of sex education among youths as reasons.

China’s family-planning system is widespread, efficient, and promotes contraception, but it has mainly targeted married couples. Today, students are increasingly turning to abortion clinics, and some of the facilities advertise in college handbooks. The Beijing Modern Women’s Hospital provides a government-subsidized “Safe & Easy A+” discount abortion for 880 yuan (US $130).

A 2009 Peking University Population Research Institute survey, funded by the UN, found that two-thirds of 22,288 Chinese ages 15-24 were accepting of premarital sex. However, most “had very limited levels of sexual reproductive health knowledge,” researchers said. Of those surveyed, 22 percent had experienced sex, but less than 50 percent used contraception at first intercourse. By comparison in a 2009
CDC survey of US high school students, 46 percent reported having sex, and 85 percent used contraception at most recent sex.

“Society is different now; it’s much more open, too open actually, and puberty is starting much younger, but schools and parents aren’t discussing these things with the kids,” said Liu Jianmin, anesthesiologist at a Xi’an abortion clinic where the majority of clients are students age 24 and younger.

“The moral outrage over having a child before marriage in our society is much stronger than the shame associated with abortion,” said Zhou Anqin, the clinic’s manager. She would like to discuss condoms and oral contraceptives during lectures at high schools and colleges, but administrators usually want her to stick with dating etiquette and menstruation. “They don’t want me to mention contraception,” she said. “They are afraid I will corrupt the students.”

**Latent TB Treatment a Greater Risk to Older Adults**  
*Reuters*, (01.10.2011) Amy Norton
The risk of treating latent TB in people age 65 and older should be carefully weighed against the risk of liver damage from treatment, a new study indicates.

Latent TB is normally kept in check by the body’s immune system, which prevents the bacteria from growing and spreading. People in whom the risk of TB activation is high include those with compromised immune systems due to HIV, autoimmune disorders, or cancer treatment. People at high risk of developing active TB may be offered treatment, typically six to nine months of isoniazid therapy. A known potential side effect of the drug is liver damage.

In the current study, Dr. Benjamin A. Smith, of McGill University, and colleagues examined government health records for Quebec’s 7.7 million residents. For the 9,145 residents treated for latent TB from 1998 to 2003, the researchers matched each case with two people the same age and sex who were not treated for the infection.

“The main goal of this study was to quantify the risk,” said Smith. “We were able to get a real-world picture, so we can give meaningful information to patients.”

The researchers found that 45 people in the TB cohort were hospitalized for liver damage, with the most common diagnosis being non-infectious hepatitis, inflammation not caused by a viral infection. Of the 45 cases, 22 were persons over 65.

The older adults in the TB group were in poorer overall health than the comparison group. But even after adjusting for conditions like cancer, diabetes, and kidney disease, those treated for latent TB were six times more likely to be hospitalized for liver damage than untreated older adults.

Smith said older latent TB patients should talk to their doctors about all the potential risks for treating or not treating the infection. For those needing treatment, one option could be monthly liver-function tests to detect any signs of damage early on. “It always boils down to the risks versus benefits for any one individual,” he said.


**Household-Level Correlates of Condom Use Among a Representative Sample of Canadian Adolescents**  
*Sexual Health Vol. 7; No. 4: P. 441-447*, (11..2010) Brandon D.L. Marshall; Mieke Koehoorn; Jean A. Shoveller
The relationship between an adolescent’s home environment and his/her likelihood of engaging in sexual risk behavior was the focus of the current study. Among a nationally representative sample of Canadian youths ages 15 to 19, the authors examined household-level correlates of condom use at last intercourse.

Logistic regression analyses were applied to data from the 2005 Canadian Community Health Survey to determine whether characteristics of the home environment were associated with self-reports of condom use during most recent intercourse.

Included in the analysis were 3,974 sexually active adolescents; 74.8 percent reported condom use at last intercourse.

After adjusting for household education and income, the researchers found that teens living in larger dwellings were less likely to report not using condoms. Those whose households included greater numbers of individuals were more likely to report not using condoms. Older age, female gender, use of
alternative contraception, and “having a weak sense of community belonging” also were identified as significant correlates of not using condoms.

“Our results demonstrate that factors related to the household environment are independently associated with condom use among adolescents,” the authors concluded. “Policies and programs that aim to promote condom use should seek to address issues such as privacy, which may limit adolescents’ ability to engage in safer sexual practices.”

**Associations Between Alcohol Misuse and Risks for HIV Infection Among Men Who Have Multiple Female Sexual Partners in Cape Town, South Africa**

AIDS Care Vol. 22; No. 12: P. 1544-1554 (12.2010) Loraine Townsend; Samantha R. Rosenthal; Charles D.H. Parry; Yanga Zembe; Catherine Mathews; Alan J. Flisher

High alcohol consumption rates occurring within the context of high HIV prevalence pose a significant public health challenge in South Africa. In their design of the current study, the authors set out to answer three questions regarding these coexisting health challenges: “(a) Are problem drinkers more likely to have multiple concurrent partners than those who are not? (b) Are condoms applied less effectively and less consistently by problem drinkers compared to those who are not? (c) Are the female sexual partners of problem drinkers different from those who are not?”

In two peri-urban settings on the outskirts of Cape Town, the researchers conducted two cross-sectional HIV bio-behavioral surveillance surveys using Respondent-Driven Sampling. The recruited participants were 848 men ages 25 to 55 who had multiple concurrent female sex partners. Men who scored three or higher on the CAGE questionnaire were classified as problem drinkers. Significant associations between outcome variables and problem drinking were assessed using multivariate logistic regression models.

Among the men, 58 percent were rated as problem drinkers. In comparison to other participants, the problem drinkers were significantly more likely to report:

- having any STD symptom
- non-use of condoms due to drinking
- inconsistent use of condoms with all partner types
- having had a “once-off” sexual relationship, and that their most recent such partner was unemployed
- that they met their most recent partner at a venue where alcohol is served.

“Alcohol may fuel once-off sexual encounters, often characterized by transactional sex and women’s limited authority to negotiate sex and condom use; factors that can facilitate transmission of HIV,” the authors concluded. “HIV prevention interventions specifically targeting drinkers, the contexts in which problem drinking occurs, and multiple sexual partnering are urgently needed.”

By Vanessa Schipani

**Variety, the spice of immunology**

Can ecologists help immunologists understand how immune responses vary in the wild? [Published 13th January 2011 02:27 PM GMT]

In humans and wild animal populations, immune responses can vary greatly between individuals, species, and environments—yet, the vast majority of immunological studies are conducted on well-fed, parasite-free, genetically similar lab mice. Recently, however, ecologists and immunologists have begun to join forces to study the long-suspected variability of immune systems in wild populations.

"Lab mice live in really happy conditions" compared to animals in the wild, said Tom Little, an evolutionary biologist at the University of Edinburgh in the UK, but "we can't just study things under really happy conditions [because] it's just not what's normal...What if everything we know about the immune system only really happened in the lab?"

Indeed, a recent comparison of the immune functions of wild and lab mice revealed that wild mice generally had stronger immune responses than their laboratory counterparts.

"There's got to be at least 100,000 papers that looked at the immune system of mice in the lab, but no more than five papers that looked at it in wild mice," said the study's lead author Mark Viney, a parasitologist at Bristol University in the UK. These differences may have a direct impact on how immunologists interpret the findings of their laboratory studies, he added.

The study of ecoimmunology, as it’s called, started in the 1990s when ecologists began to take an interest in understanding this variation in immune responses in the wild, and how it influences or is
influenced by community structure. Without a good toolbox of immunological techniques, however, early experiments were rudimentary, leading researchers to question their biological relevance. But more recently, immunologists have joined in, bringing their own perspective to the field, along with more advanced methods for the study of immunology in wild animals.

Indeed, the collaboration has already produced at least one successful field study of immunity. Working with a group of evolutionary biologist at the University of Edinburgh, immunologist Andrea Graham of Princeton University found that wild soay sheep on the Scottish island of Hirta were more likely to survive the harsh, parasite-infested winters if they had high levels of a certain kind of antibody, known as antinuclear antibodies (ANAs). However, these sheep also reproduced less frequently, suggesting a strong immune system may come at a cost.

The correlation only occurred during especially harsh winters, however, when up to 50 percent of the population dies, suggesting that immune variability may evolve more readily in fluctuating environments. The study also challenged the theory that autoimmunity only exists in lab and domesticated animals and some human populations, as the sheep expressed levels of ANAs associated with autoimmune disorders in other species.

Studying the variance of immune systems in human populations may also be enlightening, Viney said, informing research on vaccine development, for example. "Humans in developing and developed countries are mirrors of wild animals and lab animals when it comes to their relative susceptibility to disease and parasites," he said. Because immune systems function differently under the stress of disease and malnutrition, vaccines could be more effective if targeted for different populations of people.

The newfound teamwork may also benefit the immunologists, Viney added. "Mainstream immunology needs to think in an evolutionary fashion," he added. "Sometimes you have to stand back, and think of the broad picture"—something ecologists do very well.

Ecologists might help immunologists understand the microflora of the human digestive tract, for example, said Judith Allen, a professor of immunology at the University of Edinburgh. "Ecologists understand communities, and these gut bacteria are communities within our bodies," she said.

Personalized medicine may be another area ripe for collaboration, added Brian Lazzaro, an evolutionary geneticist at Cornell University. "The ability to [tailor treatments to individual patients] will obviously hinge on understanding how individuals vary immunologically and in their interactions with specific pathogens and reactions to various treatments," he said.

Though ecoimmunology may be young, it seems to be drawing more and more attention. Last year, the National Science Foundation funded a collaborative network of ecologists, evolutionary biologist, and immunologists aiming to develop new techniques and immunological research questions specific to animals in the wild. And next month, *Functional Ecology* plans to publish a special issue devoted entirely to ecoimmunology in hopes of attracting more researchers to the field.

Not everyone is convinced, however. "I'm not sure I would agree that ecoimmunology actually constitutes a field," said Lazzaro. "I think the origins are more in traditional evolutionary biology where there has been longstanding interest in selection imposed on hosts by pathogens and parasites [and] how activation of the immune system may limit other traits," like reproduction.

But with the newly developed "technological ability to apply the tools of traditional immunology in natural systems," he added, the field may really start to take shape.


By Carrie Arnold

**Malaria parasites synch with host**

*Plasmodium* microbes that cause malaria coordinate with the internal clocks of their hosts to increase their chances of survival

[Published 5th January 2011 12:01 AM GMT]

*Plasmodium* parasites responsible for deadly outbreaks of malaria synchronize their emergence and development with the circadian rhythms of their hosts to maximize their survival and spread.
The results, published online today (January 5) in *Proceedings of the Royal Society B*, give clues to why circadian clocks are maintained in so many parasite species, and may hold implications for when to administer malaria treatments to infected individuals.

"This study is incredibly important," said Deborah Bell-Pedersen, a molecular biologist at Texas A&M University, who was not involved in the study. "It helps us appreciate the role of clocks in organisms, and how they provide an advantage to their growth and well-being."

For years scientists have recognized the special timing of malaria infections: millions of *Plasmodium* parasites emerge en masse from red blood cells to cause the fever, chills, and anemia that characterize malaria. This military precision is believed to be crucial to the microbes' survival, as the host immune response that follows efficiently mops up any straggling *Plasmodium* that emerge after the group. In other words, the parasites have adopted a "safety in numbers" technique.

The symptoms of malaria, caused by the physiological stress of the parasite influx combined with the host immune response, tend to return regularly, often at the same time of day. To Sarah Reece, a malaria researcher at the University of Edinburgh in the UK, this meant that the malaria parasites must be able to tell time. Indeed, previous studies have shown that *Plasmodium* could sense their host's melatonin levels, a reliable proxy for the body's clock.

To determine how the parasites use this information, Reece and her colleagues created a mismatch between the circadian clocks of the *Plasmodium* microbes and their mice hosts. The researchers kept one group of mice on their normal light schedule of 7am to 7pm, but kept a second group of mice on a reversed, 7pm to 7am schedule. After two weeks, the team infected the mice with *Plasmodium* in the "morning"—7am for the first group and 7pm for the latter—and watched the resulting disease develop.

In both groups, the parasites emerged during normal evening hours, but in the group with a mismatch between the host and parasite internal clocks, only half as many *Plasmodium* appeared, suggesting the parasite were less likely to survive the host's massive immune response.

The circadian mismatch also halved *Plasmodium*'s ability to spread to other hosts. Before they emerge from the red blood cells, a few of the parasites differentiate into gametes that combine to form the next generation when an infected host is again bitten by a mosquito. The *Plasmodium* in the asynchronous mice, however, only produced half the number of gametes. So this circadian mismatch hits *Plasmodium* twice: it halves its ability to survive in its host, and it halves its chances of transmission.

"These results show that the [circadian] clock has had a role in the evolution of the parasite itself," Bell-Pedersen said. "This is the first time that this has been shown experimentally."

"Everything pretty much has a circadian clock, but we don't really know why," Reece said. These results help explain the evolutionary forces that have been maintaining these circadian clocks in these parasites for hundreds of millions of years.

While interesting, the finding won't necessarily translate into new malaria treatments, said Bell-Pedersen, but the results may have implications for the timing of existing malaria treatments. Therapies may work better, for example, if the medication is given at different times, or if the patients are placed on different light/dark schedules, she said.

Furthermore, the findings may apply to other types of infections, Reece said. If other parasites have this need to synchronize with their hosts, "then this might be something to use to treat all kinds of diseases," she said.


Comment:
Previous work on bird malaria
by Robert McLean, [Comment posted 2011-01-07 12:54:36]
This phenomena was shown to occur with avian malaria a number of years ago. The avian plasmodium parasite was able to sustain
its population within avian host populations at specific locations through synchronized relapse in local, previously infected birds
following their migratory return to breeding grounds in the spring by responding to physiological changes in the birds from both the
migratory journey and reproductive activity that occurred in synchrony with the initiation of spring breeding activity and emergence
of the local vector mosquitoes.

A Model For The Ecology Of Avian Malaria. RICHARD L. BEAUDOIN, JAMES E. APPLEGATE, DAVID E. DAVIS, ROBERT G.

Suggestion for using this information to treat malaria
by Steven Pace, [Comment posted 2011-01-06 18:17:12]
Melatonin is cheap, and widely available. Of course blocking blue light will cause natural production of melatonin. If melatonin is
malaria's chosen "swarm release trigger", and we know this, we can manipulate it.

My suggestion is that you raise melatonin levels, then lower them, with a frequency higher than normal day/night. If the
frequency is high enough, it will cause some of the plasmodium to release before the rest is ready for release. The result would be a
flattening of the "swarm", and the immune system would "mop them up".

Malaria parasite
by Nirmal Mishra, [Comment posted 2011-01-05 20:15:16]
Synchronicity of Plasmodium with the host
Synchronicity is one of the hallmarks of host-parasite relationships.
There is always a fine-tuning between the two so that the parasite gets the advantage and lives in quietly to reproduce in tremendous
numbers. Only when a balance is tilted is there a problem. In this article what is shown is the manner in which Plasmodium picks
the clue as to the day-night cycle manifested through the pineal hormone. The periodicity of P. vivax, P. ovale, P. malaria, and P.
falciparum may also have an intrinsic and extrinsic basis.

Nirmal Kumar Mishra
Retd. University Professor of Zoology, Patna University, Patna (India)

Five Things About HIV They're Not Telling You
By Mark S. King
January 12, 2011
In the early 1990s, I was invited to participate on a roundtable with national HIV/AIDS public health
officials. They wanted to gauge what those on the front lines were thinking about HIV prevention
campaigns. I gave them an earful.

"Why won’t you tell gay men that being a top is less risky?" I lamented. They always publicly resisted
"promoting" anything that might conceivably transmit HIV, no matter how remote the odds, and that
attitude drove me nuts. "When you don’t acknowledge what gay men already suspect," I told them, "you
lose credibility! Give us something to feel better about engaging in... won’t you even say that oral sex
is a lot safer? Why can’t you throw gay men a bone?"

Gay men are still forced to piece together the latest facts about HIV, largely due to the reticence of
public health messages—or just plain homophobia.

Thank goodness for people like Sean Strub, lifelong AIDS activist and founder of POZ Magazine. In
his blog posting on Poz.com last month, Sean joined a chorus of advocates who are furious
over a fearful New York City public health commercial. The spot says "it’s never just HIV," and shows horrific HIV
outcomes that include broken bones, insanity and even a gruesome shot of anal cancer.

Sean sees the campaign as another example of how public health gets it wrong, investing in failed
"fear-based" messages while keeping a lid on information that could make a real difference.

In this video episode of My Fabulous Disease, Sean and I discuss five things we believe either
represent what is wrong with prevention campaigns, or what strategies are being ignored by public health
officials. Pay attention to my links in this post, because I document the research and campaigns we
discuss.

We refer to Swiss experts who suggest people with HIV with undetectable viral loads may be non-
infectious. We discuss an infamous 1987 Australian commercial called "The Grim Reaper," and refer to
research that concludes that fear-based messages do not change long-term behavior.

You might enjoy comparing the difference between the NYC "It's Never Just HIV" spot (in all its
frightful foreboding) to the life-affirming Japanese campaign "Little Taiko Boy," which presents sexuality
in a straightforward manner (complete with music and sexy-time lyrics!).

Does anything in our talk surprise (or offend) you? Did you know HIV negative people could take a
drug regimen immediately after exposure (sexual and otherwise) and greatly reduce the risk of becoming
infected? Do you agree that stigma against those living with HIV may be greater now than ever before?
This is an important community discussion, and I hope you will consider sharing this with friends and
colleagues. I'm always up for constructive debate or dissent.
Meanwhile, my friends, please be well.
**Female Sexual Partners of Injection Drug Users in Vietnam: An At-Risk Population in Urgent Need of HIV Prevention Services**

*AIDS Care Vol. 22; No. 12: P. 1466-1472*, (12..2010)  Theodore M. Hammett; Nghiem Thi Ha Van; Ryan Kling; Kieu Thanh Binh; Khuat Thi Hai Oanh

HIV prevalence among injection drug users in Vietnam is approximately 30 percent, a factor driving the nation’s epidemic. “Most IDUs are sexually active and may infect their female sexual partners (SPs),” the authors wrote, adding, “Male dominance in sexual decisions is deeply embedded in Vietnamese culture.” Although SPs represent “an important potential bridging population,” few HIV prevention interventions have targeted them.

The current study discusses findings from a baseline survey of SPs conducted in 2008 in Hanoi, where peer-based HIV prevention interventions for this population now are being implemented. HIV prevalence among the Hanoi SPs was 14 percent, according to the survey, and only 27 percent of the women reported condom use with their primary male partner at least half the time.

Despite the fact that 69 percent of the SPs were in a serodiscordant relationship or did not know their partner’s status, condom use was no more frequent among these couples than among those whose HIV status was concordant. Many SPs said they were afraid to provoke their partner by requesting condom use. This was even more likely to be true in the case of serodiscordant or unknown status relationships. Limited prior access to HIV prevention services was reported by the SPs.

“Many SPs in Vietnam are at high risk for HIV and in need of HIV prevention interventions,” the authors concluded. “However, to date, this population has been seriously underserved. Our interventions are in progress, and results will be reported subsequently.”

**Gay Men’s Perceptions of Sexually Transmissible Infections and Their Experiences of Diagnosis: ‘Part of the Way of Life’ to Feeling ‘Dirty and Ashamed’**

*Sexual Health Vol. 7; No. 4: P. 411-416*, (11..2010)  Martin Holt; Diana Bernard; Kane Race

The authors introduced the current study by noting that while gay men are more likely than their heterosexual peers to be diagnosed with a sexually transmitted infection, little research has focused on gay men’s perceptions of STIs other than HIV. Using information from interviews conducted with gay men in Sydney, the team analyzed participants’ perceptions of STIs and their experiences of testing and diagnosis.

More than half the men reported having ever been diagnosed with an STI. The infections “were generally regarded as inconvenient consequences of sexual activity.” Compared to curable bacterial STIs, recurring viral STIs were perceived as more serious. All STIs were thought of as “considerably less important than HIV.” To manage STI risk, the most commonly employed strategies were condom use and regular testing.

“Despite the relative lack of concern attributed to STIs, being diagnosed with an STI could generate feelings of shame, embarrassment, and annoyance,” the team wrote. Among some respondents, educational campaigns to destigmatize STIs and promote regular testing appeared to have been effective.

“We believe that to maintain high rates of STI testing among gay men, community education efforts should continue to reduce the stigma associated with STIs, and greater support should be offered to gay men when they receive an STI diagnosis,” the authors concluded.

**Aerosols transmit prions to mice, causing disease**

Scientists at the University of Zurich (Switzerland) and the Federal Research Institute for Animal Health (FLI; Tuebingen) have challenged the notion that airborne prions are innocuous. Details of how inhalation of prion-tainted aerosols induced disease are published January 13 in the open-access journal *PLoS Pathogens*.

It is known that prions can be transmitted through contaminated surgical instruments and, more rarely, through blood transfusions. However, prions are not generally considered to be airborne—in contrast to many viruses such as influenza and chicken pox.

In the new study, the authors housed immunodeficient and immunocompetent mice in special inhalation chambers and exposed them to prion-containing aerosols, which induced disease. Exposure to aerosols for one minute was sufficient to induce disease in 100% of mice. The longer the exposure, the shorter the incubation time in the recipient mice, after which they developed the clinical signs of a prion
disease. These findings indicate that prions are airborne. Prions appeared to transfer from the airways and colonize the brain directly, since various immune system defects – known from previous experiments to prevent the passage of prions from the gut to the brain – did not prevent infection.

The prion is the infectious agent that caused the epidemic of “mad cow” disease, also termed bovine spongiform encephalopathy (BSE). BSE claimed the life of more than 280,000 cows in the past decades. Transmission of BSE to humans, e.g. by ingestion of food derived from BSE-infected cows, causes variant Creutzfeldt-Jakob disease which is characterized by a progressive and invariably lethal breakdown of brain cells. Consumption of food made from BSE-infected cows has caused the deaths of almost 300 people.

The precautionary measures against prion infections in scientific laboratories, abattoirs, and animal feed factories have not typically included stringent protection against aerosols. These new findings suggest that it may be advisable to consider the possibility of airborne prion transmission, and to create regulations aimed at minimizing the prion infection risks to humans and animals.


The microbes in our gut regulate genes that control obesity and inflammation

New research in the FASEB Journal suggests that the absence of intestinal toll-like receptor 2 affects gut bacteria, pointing to a new way to manage weight and intestinal problems

If you are looking to lose weight in the coming year, you may need help from an unexpected place: the bacteria in your gut. That's because scientists have discovered that the bacteria living in your intestines may play a far more significant role in weight loss and gastrointestinal problems than ever imagined. In a new research report published online in The *FASEB Journal* (http://www.fasebj.org), researchers show that a deficiency of Toll-like receptor 2 (Tlr2)—used by mammals (including humans) to recognize resident microbes in the intestines—leads to changes in gut bacteria that resemble those of lean animals and humans. This discovery builds on previous research demonstrating that a deficiency of TLR2 protects against obesity, while at the same time promoting gastrointestinal problems like excessive inflammation. It also shows that genes controlling TLR2 expression play a very important role in one's gastrointestinal health and weight management.

"Our work highlights the remarkable capacity for an orchestrated reprogramming of the intestinal inflammatory network to overcome significant genetic challenges in the mammalian bowel," said Richard Kellermayer, Ph.D., a researcher involved in the work from the Section of Pediatric Gastroenterology, Hepatology and Nutrition at Baylor College of Medicine in Houston. "The appropriate exploitation of this remarkable capacity may provide means for the prevention and optimized treatment of common metabolic (such as obesity and diabetes) and gastrointestinal disorders."

To make this discovery, Kellermayer and colleagues studied normal mice and mice deficient in TLR2 using the large intestinal lining of these mice. They compared the TLR2-deficient ones to the normal group, as well as the bacteria, the epigenome (more specifically DNA methylation, a molecular change in the DNA associated with decreased gene expression), and the gene expression of the animals. The researchers found that the absence of TLR2 leads to microbial changes in the gut that resemble lean animals and humans, as well as immunologic changes similar to those observed in ulcerative colitis.

"Every New Year, a significant percentage of us resolve ourselves to lose weight," said Gerald Weissmann, M.D., Editor-in-Chief of The *FASEB Journal*. "but national statistics on obesity show that we're failing fast. This research linking gut bacteria to TLR2 expression opens entirely new doors for weight control solutions, first by cementing TLR2 as a drug target for obesity, and second by providing further evidence that managing gut bacteria may be an important and effective way to control weight. The challenge, of course, is to find a way to tip the scales just enough to keep weight under control without causing serious gastrointestinal problems."

**Measles Virus, a Weapon Against Cancer?**

ScienceDaily (Jan. 11, 2011) — When most people in the developed world think of measles, what comes to mind is only a dim memory of a vaccination at a pediatrician’s office. But while childhood vaccination has virtually eliminated measles from North America and much of Europe, researchers remain interested in the virus.

This fascination persists partly because improving the measles vaccine could help eliminate the more than 10 million measles infections and 150,000 measles-caused deaths that still occur worldwide. But it
also has another source: Scientists believe that modified measles viruses can be "re-targeted" to attack only tumor cells, and thus transformed into a powerful new therapy for cancer.

Now, a new discovery about the process by which measles invades cells has brought the dream of transforming the virus into a weapon against cancer one step closer to reality. A research team including scientists from the University of Texas Medical Branch at Galveston and the Mayo Clinic in Rochester, Minn. have produced a detailed picture of the intricate molecular mechanism that measles virus uses to attach to and enter the cells it infects.

The key players are two proteins that form the spherical envelope surrounding the genetic material of the measles virus. One is an attachment protein that binds to receptor molecules on the outer membrane of a host cell, and the other is a fusion protein that merges the viral envelope with the cell membrane, enabling the virus to infect the cell. The study, published in the recent issue of *Nature Structural Biology & Molecular Biology* demonstrated that the intrinsic flexibility of the attachment protein is a necessary condition to initiate the cell fusion process.

"The overall goal of our Mayo Clinic collaborator, Roberto Cattaneo, is to redirect the measles virus to attack specific cancer cells, and to accomplish that he and his group need to know as much as they can about the mechanisms of measles infection," said UTMB professor Werner Braun, an author of the study. "We have a long-standing collaboration with his group, using our theoretical predictions and computational methods to help them better target their experimental work."

UTMB Health research scientist Numan Oezguen used computer-based molecular modeling to predict interaction sites and suggested specific mutations that would alter the interaction and mobility of the attachment protein heads. Results of these experiments performed by the Mayo Clinic team—led by Cattaneo—showed that cell entry of the measles virus depends on a twisting motion of the attachment protein's heads.

To produce an accurate portrait of the dynamic mechanism the Mayo Clinic group created measles viruses with mutations affecting the mobility of their attachment protein heads, and then tested the mutated viruses to determine each type's ability to infect cells. "What Dr. Cattaneo's experiments showed was that the motion of these two parts of the attachment protein has a dramatic effect on infectivity," Braun said. "In a simplified sense, we think this works like a lever—if the cell receptors pull on the attachment protein properly, they generate this type of motion, and this triggers the fusion protein and leads to infectivity."

**Journal Reference:**

**Virus Killer Gets Supercharged: Discovery Greatly Improves Common Disinfectant**

ScienceDaily (Jan. 12, 2011) — A simple technique to make a common virus-killing material significantly more effective is a breakthrough from the Rice University labs of Andrew Barron and Qilin Li.

Rather than trying to turn the process into profit, the researchers have put it into the public domain. They hope wide adoption will save time, money and perhaps even lives.

The Rice professors and their team reported in *Environmental Science and Technology*, an American Chemical Society journal, that adding silicone to titanium dioxide, a common disinfectant, dramatically increases its ability to degrade aerosol- and water-borne viruses.

"We're taking a nanoparticle that everyone's been using for years and, with a very simple treatment, we've improved its performance by more than three times without any real cost," said Barron, Rice's Charles W. Duncan Jr.-Welch Professor of Chemistry and a professor of materials science. Barron described himself as a "serial entrepreneur," but saw the discovery's potential benefits to society as being far more important than any thoughts of commercialization.

Barron said titanium dioxide is used to kill viruses and bacteria and to decompose organics via photocatalysis (exposure to light, usually ultraviolet). The naturally occurring material is also used as a pigment in paints, in sunscreen and even as food coloring.

"If you're using titanium dioxide, just take it, treat it for a few minutes with silicone grease or silica or silicic acid, and you will increase its efficiency as a catalyst," he said.

Barron's lab uses "a pinch" of silicon dioxide to treat a commercial form of titanium dioxide called P25. "Basically, we're taking white paint pigment and functionalizing it with sand," he said.

Disinfecting a volume of water that once took an hour would now take minutes because of the material's enhanced catalytic punch, Barron said. "We chose the Yangtze River as our baseline for testing,
because it’s considered the most polluted river in the world, with the highest viral content,” he said. "Even at that level of viral contamination, we’re getting complete destruction of the viruses in water that matches the level of pollution in the Yangtze."

Using a smaller amount of treated P25 takes longer but works just as well, he said. "Either way, it’s green and it’s cheap."

The team started modifying titanium dioxide two years ago. Li, an assistant professor in civil and environmental engineering whose specialties include water and wastewater treatment, approached Barron to help search for new photocatalytic nanomaterials to disinfect drinking water.

The revelation came when students in Barron’s lab heated titanium dioxide, but it wasn’t quite the classic "aha!" moment. Graduate student and co-author Michael Liga saw the data showing greatly enhanced performance and asked fellow graduate student Huma Jafry what she had done. Jafry, the paper’s first author, said, "I didn't do anything," Barron recalled.

When Barron questioned Jafry, who has since earned her doctorate, he discovered she used silicone grease to seal the vessel of P25 before heating it. Subsequent testing with nonsilicone grease revealed no change in P25’s properties, whether the sample was heated or not. Remarkably, Barron said, further work with varying combinations of titanium dioxide and silicone dioxide found the balance between the two at the time of the discovery was nearly spot-on for maximum impact.

Barron said binding just the right amount of silica to P25 creates an effect at the molecular level called band bending. "Because the silicone-oxygen bond is very strong, you can think of it as a dielectric," he said. "If you put a dielectric next to a semiconductor, you bend the conduction and valence bands. And therefore, you shift the absorption of the ultraviolet (used to activate the catalyst)."

Bending the bands creates a path for electrons freed by the UV to go forth and react with water to create hydroxyl radicals, an oxidant responsible for contaminant degradation and the most significant reactive agent created by titanium dioxide. "If your conduction band bends to the degree that electrons find it easier to pop out and do something else, your process becomes more efficient," Barron said.

Li saw great potential for enhanced P25. In developed countries, photo reactors designed to take advantage of the new material in centralized treatment plants could more efficiently kill bacteria and inactivate viruses in water supplies while minimizing the formation of harmful disinfection byproducts, she said.

But the greatest impact may be in developing nations where water is typically disinfected through the SODIS method, in which water is exposed to sunlight for its heat and ultraviolet radiation. "In places where they don’t have treatment plants or even electricity, the SODIS method is great, but it takes a very long time to make water safe to drink," Li said. "Our goal is to incorporate this photocatalyst so that instead of taking six hours, it only takes 15 minutes."

Barron wants to spread the good news. "Here’s a way of taking what is already a very good environmental catalyst and making it better," he said. "It works consistently, and we've done batch after batch after batch of it now. The methodology in the paper is the one we routinely use. As soon as we buy P25, we treat it."

Journal Reference:

New Research Aims to Shut Down Viral Assembly Line
ScienceDaily (Jan. 12, 2011) — Under the electron microscope, a coronavirus may resemble a spiny sea urchin or appear crownlike, (the shape from which this family of pathogens takes its name). Previously recognized as the second leading cause of the common cold in humans and for economically important diseases in many domesticated animals, a new disease form abruptly emerged as a major public health concern in 2002, when the SARS coronavirus (CoV) surfaced in Asia.

The rapid spread of the virus caused significant social and economic disruption worldwide, infecting over 8000 people with Sudden Acute Respiratory Syndrome or SARS and killing about 10 percent of them. While SARS-CoV was brought under control through decisive action by health officials, the sudden scourge underlined the threat posed by coronaviruses and spurred new research into the inner workings of these infectious agents.

Brenda Hogue and her colleagues at the Biodesign Institute at Arizona State University are studying the intricate formation of these viruses—a process known as viral assembly. The research may offer fresh insight, leading to a new generation of antiviral agents that can disrupt the ability of coronaviruses like...
SARS to assemble viable infectious particles. Such strategies may prove applicable against other classes of virus as well.

The group's work recently appeared in the *Journal of Virology*.

Viruses, Hogue stresses, differ fundamentally from other common microscopic pathogens like bacteria, in that viruses are structurally primitive, lacking the means to independently replicate. Viruses are composed of genetic information (DNA or RNA), encased by proteins. They exist in a shadowy region between living and non-living entities.

In order for a virus to replicate, it must commandeer machinery of a host cell it has infected. Nevertheless, viruses have evolved to be highly adept at this sort of replication-by-proxy, and can infect virtually all types of organisms, from animals and plants to bacteria and even Archaea. Viruses—of which millions of forms are known to exist—are far and away the most numerous (and successful) parasitic invaders on earth.

"Coronaviruses are a very large family of RNA viruses," Hogue says. "They infect humans and a broad range of animals." While the symptoms produced by coronavirus infection in humans tend to be respiratory, in animals, such viruses can cause a range of severe problems, from neurological ailments to immunosuppressive effects. Various coronaviruses are responsible for common colds in humans, though the combined upper and lower respiratory symptoms and gastrointestinal complications seen in SARS patients are unusual.

In the study reported in *Journal of Virology*, Hogue and her team closely examined one of the major proteins found in the coronavirus that is crucial to the pathogen's process of assembly. Known as the M, it is one of four proteins, in addition to S, N and E, required to produce a fully assembled viral particle, capable of infecting a host.

The membrane (M) protein makes up the bulk of the outer shell or envelope of the virus, forming a lattice that surrounds and shields the viral genome. The spike protein (S)—named for its spike-like or crown-like appearance under electron microscopy, is critical for allowing the coronavirus to attach to the host cell's receptors, prior to viral entry into the cell. The nucleocapsid (N) protein encapsidates the genomic RNA. The envelope or E protein is the least plentiful protein known to play a central role in virus assembly, though its presence is very important. In addition to assisting viral assembly, the E protein also appears to be involved in shuttling the newly assembled virions out of the cell, enabling these particles to escape and infect other host cells in the exponential process of viral infection.

The group wanted to determine the requirements for the M protein to function during assembly of the viral envelope. To establish this, coronaviruses were genetically manipulated to form mutant versions, exhibiting varying degrees of viability. Much of this manipulation focused on domains within the viral genome coding for a distinct structural and/or functional domain of the M protein. Conserved domains, as they are known, contain genetic sequence patterns or motifs that tend to recur across a number of different viruses or within a particular virus type, like catch phrases recurring in different books. These conserved domains are generally involved in functions essential to viral formation, survival or replication, making them an attractive target for therapeutic efforts designed to short-circuit viral assembly.

Viral pathogens like the SARS coronavirus, (along with hepatitis C and influenza), use RNA rather than DNA as their genetic material. In general, such RNA viruses mutate more rapidly than DNA viruses, posing particular challenges to virologists hoping to combat them. They can also acquire alterations that allow them to hop from one species to another. Something like this now appears to be at the root of the SARS outbreak.

"We think that the reservoir for this virus is bats, because a large number of SARS-like viruses have been isolated from bat populations around the world," Hogue says. SARS-CoV was subsequently able to infect a secondary animal host, now believed to be the civet cat—a mongoose-like creature found in Asia and sometimes used as a food source, particularly in China, where the SARS outbreak originated. Contact with infected civets in the open markets may have caused the initial human cases of SARS, which then rapidly spread—human to human—from the Guangdong provinces in China to 37 countries.

Viruses that act as respiratory pathogens, including SARS, are highly transmissible from person to person through contact with respiratory droplets that become aerosolized from coughs or sneezes. Virions may also persist on surfaces that come in contact with an infected individual. Following transmission, virions initiate the infectious process of host cells, which transpires in several important phases.

First, viral proteins located on the virus' outer capsid bind to particular receptors on the host cell's surface. Next, virions enter the cell, either by fusing their membranes with those of the host cell or through the process of endocytosis, in which the host cell takes in the virion in a membrane-bound vesicle. The virion is now in a position to begin the replication cycle, releasing its genetic material into the
cell. The viral genome encodes genes that when expressed, yield the protein components necessary to assemble new virus particles.

Hogue stresses the importance of in silico analysis, in which large libraries of proteins can be screened through analysis, in order to identify conserved and non-conserved protein regions, thus greatly accelerating the pace of discovery. "The more we learn about these particular regions of proteins that are critically important for the assembly process," she says, "the likelier it is we can design molecules that will be able to interfere with this process."

While some conserved domain alterations in the M protein proved lethal to coronaviruses, others undermined viral assembly without shutting it down completely, often causing compensatory efforts on the part of the virus, (known as second site changes) which may offer insights into the virus’ adaptive capabilities. In the coming year, Hogue plans to examine the non-lethal changes introduced, studying these mutant viruses under high-resolution cryo-EM, to determine how alterations of specific domains affect overall coronaviral structure.

Additionally, Hogue's group is closely examining the under-represented envelope or E protein. "One reason we are excited about this is that a number of enveloped viruses, including hepatitis C, influenza and others, that are of real medical significance, have small ion channel proteins," Hogue says. "If we can develop ways to target and obliterate the ion channel activities of these proteins, we may be able to disable these viruses and prevent or reduce infections."

**Study Evaluates Clinical Outcome of HIV-Infected Patients with Discordant Virological and Immunological Response to Antiretroviral Therapy**

“A subgroup of human immunodeficiency virus type 1 (HIV-1)-infected patients with severe immunodeficiency show persistently low CD4+ cell counts despite sustained viral suppression. It is unclear whether this immunovirological discordance translates into an increased risk for clinical events. ... Data [were analyzed] from a large multicenter cohort incorporating 14,433 HIV-1-infected patients in Germany. Treatment-naive patients beginning antiretroviral therapy (ART) with CD4+ cell counts <200 cells/µL who achieved complete and sustained viral suppression <50 copies/mL (n = 1318) were stratified according to the duration of immunovirological discordance (failure to achieve a CD4+ cell count ≥200 cells/µL). ... During a total of 5038 person years of follow-up, 42 new AIDS events occurred. The incidence rate of new AIDS events was highest in the initial 6 months of complete viral suppression ... and decreased significantly by 65% per year in patients with immunovirological discordance .... Immunovirological discordance and prior AIDS diagnosis were independently associated with new AIDS events ... . [Researchers suggest that compared] with immune responders, patients with immunovirological discordance seem to remain at increased risk for AIDS [and that absolute] risk is greatly reduced after the first 6 months of complete viral suppression."

**Results Reported on the Association of Age and Comorbidity with Physical Function in HIV-Infected and Uninfected Adults**

“HIV clinical care now involves prevention and treatment of age-associated comorbidity. Although physical function is an established correlate to comorbidity in older adults without HIV infection, its role in aging of HIV-infected adults is not well understood. To investigate this question we conducted cross-sectional analyses including linear regression models of physical function in 3227 HIV-infected and 3240 uninfected patients enrolled 2002-2006 in the Veterans Aging Cohort Study-8-site (VACS-8). ... Across the age groups decline in physical function per year was greater in HIV-infected patients ... compared to uninfected patients .... This difference, although statistically significant (p < 0.01), was small. Function in the average 50-year-old HIV-infected subject was equivalent to the average 51.5-year-old uninfected subject. History of cardiovascular disease was a significant predictor of poor function, but the effect was similar across groups. Chronic pulmonary disease had a differential effect on function by HIV status .... . A 50-year-old HIV-infected subject with chronic pulmonary disease had the equivalent level of function as a 68.1-year-old uninfected subject with chronic pulmonary disease. We conclude that age-associated comorbidity affects physical function in HIV-infected patients, and may modify the effect of aging. Longitudinal research with markers of disease severity is needed to investigate loss of physical function with aging, and to develop age-specific HIV care guidelines.”
RTS,S Offers 46 Percent Protection Against Malaria For At Least 15 Months After Vaccination, Study Finds

Friday, January 14, 2011
A Phase II trial published Friday in *Lancet Infectious Diseases* has shown that RTS,S, the "experimental malaria vaccine from GlaxoSmithKline provides African children with long-lasting protection" against malaria, Reuters reports. "Scientists conducting the mid-stage trial at the Kenya Medical Research Institute said results showing the shot offered 46 percent protection for 15 months meant it had 'promise as a potential public health intervention against childhood malaria in malaria endemic countries'," the news service notes (Kelland, 1/14).

"The findings suggest [GlaxoSmithKline] may have succeeded where others have failed in developing the world's first effective shot against the deadliest mosquito-borne disease," Bloomberg Businessweek writes. "Glaxo expects to have the results of final-stage trials by late this year or early next, Chief Executive Officer Andrew Witty said in October."

"We've never had a malaria vaccine get this far in its development and continue to show such promise," Director of the WHO Global Malaria Program Robert Newman said. "It's promising and encouraging" (Bennett, 1/13).

For the study, between March 2007 and October 2008, researchers randomly assigned 894 children five to 17 months from Kenya and Tanzania to doses of the GlaxoSmithKline vaccine, also known as Mosquirix, or a rabies vaccine, according to a Lancet press release. "Blood samples were taken before vaccination and at regular intervals during the trial to test for antibodies," the release states.

Initial tests of the RTS,S, published in 2008 showed the vaccine provided 53 percent protection against malaria for at least eight months, and scientists were interested if the vaccine provided a similar level of protection after an additional seven months (1/13).

The Telegraph reports: "After 15 months, those who had [received] the malaria vaccine were [45.8] percent less likely to have been infected with the [malaria parasite] P. Falciparum parasite than the control group. Only 11.4 percent of those given the vaccine developed clinical malaria, compared to 19.7 percent of the other group."

The vaccine works by attacking the parasite when it first enters the bloodstream or liver cells, with the aim of completely preventing infection of red blood cells (Adams, 1/14).

"RTS,S/AS01E provides sustained protection from clinical malaria over a period of 15 months (range 12 – 18 months) in young children residing in malaria endemic areas. ... Furthermore, we recorded no waning in efficacy during the trial," the authors of the study write (Olotu et al., 1/14).

"The most common adverse events were pneumonia, fits with fevers and stomach inflammation, with fewer events reported among children who received the malaria vaccine compared with those who got the rabies shot," Bloomberg Businessweek adds (1/13).

The study authors also note, "A limitation of our study is that we recruited healthy children only; further studies are needed to establish vaccine efficacy in, for example, children with HIV infection or those who are malnourished. Furthermore, phase 3 studies should include study sites at different transmission intensities to confirm how generalisable our results are" (Olotu et al., 1/14).

"Late-stage trials of the [RTS,S] in 16,000 children in seven countries across Africa are ongoing, with immunisations due to end next month," Reuters writes. "GSK chief executive Andrew Witty has said that if RTS,S proved effective in final-stage trials it would be sold at a price that those who need it most can afford. The company has said it was planning for a profit margin of 5 percent over the cost of making the vaccine, and that would be reinvested in new vaccines for malaria and other neglected diseases," according to the news service (1/14).

"Assuming results of the next trial are positive, Glaxo plans to seek regulatory approval for the shot in Europe, Stephen Rea, a spokesman, said in a telephone interview," Bloomberg Businessweek writes. "The WHO wants to wait for data on the effectiveness of the vaccine after 30 months, due in 2014, before it makes a policy recommendation on the vaccine, Newman said" (1/13).

An accompanying *Lancet Infectious Diseases Comment* also reflects on the results of the trial (Greenwood, 1/14).

Britain Boosts Funds for Hepatitis C-Infected Patients

*Agence France Presse*, (01.10.2011)
On Monday, Britain’s government announced it will provide more support for patients infected with hepatitis C virus through state health services in the 1970s and 1980s. Approximately £100 million to
£130 million (US $159 million to $203 million) in additional support will be provided over the next five years for patients with serious liver disease linked to HCV infection through blood products or transfusions during the period.


Among hemophiliacs, 4,675 were infected through blood products or transfusions supplied by the National Health Service. Of these patients, 2,807 are still alive. Another 1,300 were infected with HIV.

The most seriously ill will be given a new sum of £12,800 (US $20,266) annually in addition to a lump sum now doubled to £50,000 (US $79,164). A three-month compensation review also resulted in the government’s decision to provide funding to charities that offer counseling and to cover any prescription fees.

“Taken together, these announcements represent a significant rise in the support available to those affected by this tragedy,” Health Secretary Andrew Lansley told Parliament. In a separate statement, he said, “I fully recognize that the unintended and tragic consequences of these treatments have seriously impaired the lives of many people, together with those of their families.”

**Symptoms Are Highly Prevalent Among HIV Outpatients and Associated with Poor Adherence and Unprotected Sexual Intercourse**

*Sexually Transmitted Infections Vol. 86; No. 7: P. 520-524*, (12..2010)  Richard Harding; Fiona C. Lampe; Sally Norwood; Heather Leake Date; Claudine Clucas; Martin Fisher; Margaret Johnson; Simon Edwards; Jane Anderson; Lorraine Sherr

Noting the scarcity of data on the prevalence and burden of pain and symptoms among HIV patients in the era of antiretroviral therapy (ART), the authors set out to measure symptom prevalence and determine associations with key variables: demographics, treatment status, adherence, and risk behaviors.

In five HIV outpatient clinics in London and the southeast region of the United Kingdom, researchers administered a cross-sectional self-completed questionnaire. The subjects were consecutive patients who accepted the invitation to participate by responding to clinical and behavioral variables including the memorial symptom assessment schedule (short form). Four multivariable models were used to examine the relationship between dependent variables of psychological, physical, global symptom burden scores, number of symptoms, and key independent variables. A total of 778 patients, 77 percent of those approached, took part in the research.

Physical and psychological symptoms were “highly prevalent” among respondents, the authors found. In the preceding seven days, the proportion of patients experiencing particular symptoms was as follows: lack of energy, 70.8 percent; worry, 69.9 percent; diarrhea, 53.6 percent; sexual dysfunction, 53.5 percent; and pain, 53.2 percent. Multivariable analysis found unprotected sexual intercourse with a partner of unknown HIV status and poorer adherence to ART were significantly and independently associated with psychological symptom burden. A significant association was noted between lower educational achievement and increasing physical, psychological, and global symptom burden scores, and a higher number of symptoms. Taking ART was not found to be associated with any symptom distress measure.

“In the era of treatment, patients continue to experience high prevalence and burden of psychological and physical symptoms, which are not associated with treatment status,” the authors concluded. “Attention to these distressing problems is essential and may enhance quality of life and adherence, and minimize risk behavior. Symptoms are highly prevalent among HIV outpatients and associated with poor adherence and unprotected sexual intercourse.”

**STD Screening of HIV-Infected MSM in HIV Clinics**

*Sexually Transmitted Diseases Vol. 37; No. 12: P. 771-776*, (12..2010)  Karen W. Hoover and others

National guidelines recommend asymptomatic routine STD screening for HIV-positive patients. The researchers undertook the current study to learn whether these guidelines are being followed by providers caring for HIV-positive men who have sex with men.

By abstracting medical records at eight large HIV clinics in six US cities, the authors estimated the number of men who underwent at least one test for syphilis, chlamydia (urethral and/or rectal), or gonorrhea (urethral, rectal and/or pharyngeal) in 2004, 2005, and 2006. Nucleic acid amplification testing of both urethral swabs and urine was included in the urethral testing. The researchers further calculated the positivity for syphilis, chlamydia, and gonorrhea among the men who were screened.
The medical records of 1,334 HIV-positive MSM making 14,659 clinic visits from 2004 to 2006 were abstracted. During this period, the annual screening rate for syphilis ranged from 66 percent to 75.8 percent. Despite moderate to high positivity of specimens from asymptomatic patients (3 percent to 9.8 percent), annual screening rates for rectal chlamydia and rectal and pharyngeal gonorrhea ranged from 2.3 percent to 8.5 percent. Annual urethral chlamydia and gonorrhea screening rates of 13.8 percent to 18.3 percent were higher than rates for nonurethral sites but were still suboptimal.

“Most asymptomatic HIV-infected MSM were screened for syphilis, indicating good provider adherence to this screening guideline. Low screening rates for gonorrhea and chlamydia, especially at rectal and pharyngeal sites, suggest that substantial barriers exist for complying with these guidelines,” the authors concluded. “The moderate to high prevalence of asymptomatic chlamydial and gonococcal infections underscores the importance of screening. A range of clinical quality improvement interventions are needed to increase screening, including increasing the awareness of nucleic acid amplification tests for nonurethral screening.”

Vaccine Sharply Cuts Risk of Shingles in Seniors, Study Finds

A Kaiser Permanente study of Zostavax shows the vaccine against herpes zoster can reduce the incidence of painful shingles outbreaks by 55 percent, even in the oldest populations. The varicella zoster virus causes chickenpox and shingles, and can remain dormant in a person’s body for decades before erupting. The most severe complication is post-herpetic neuralgia, in which the virus causes inflammation inside nerves—a persistent, painful condition that is “extremely challenging to control,” said infectious-disease expert Dr. Bruce Hirsh of New York’s North Shore University Hospital, who was not involved in the study. Zostavax, made by Merck & Co., was introduced in 2006; it currently reaches only about 11 percent of the US elderly population. CDC recommends the vaccine for all people over age 60 unless they are immune-suppressed, are HIV-positive, have leukemia or lymphoma or are allergic to any of the vaccine’s components.

RNA Interference Combination Strategy Shows Promise in Laboratory Study

**SUMMARY:** Investigators from Johnson and Johnson have devised a set of short hairpin RNA sequences that may be able to inhibit nearly 90% of all known HIV strains, according to findings published in the [January 13, 2011 online edition of the open-access journal AIDS Research and Therapy](http://www.aidsresearchandtherapy.com/content/4/1/1). While HIV can mutate to develop resistance to RNA interference—as it does to conventional antiretroviral drugs—combining 4 or more highly conserved hairpin RNA segments may maintain long-term viral suppression.

Below is the text of a media advisory issued by AIDS Research and Therapy publisher BioMed Central describing the research.

**Suppression of Entire HIV Subtypes Could Now Be Possible with Multiple shRNAs**

The hope of finding new, effective drugs to treat HIV infection by launching a manifold attack on the viral genome has significantly increased, thanks to new research published in BioMed Central's open access journal AIDS Research and Therapy. HIV is a particularly difficult virus to tackle because it mutates very rapidly. Traditional drugs are often swiftly overcome by the virus, which has in part resulted in the many different variants currently circulating.

Australian researchers from Johnson and Johnson Research Pty Ltd have been studying new ways to fight HIV by exploiting the recently discovered a gene-silencing mechanism called RNA interference (RNAi). They have created hundreds of small molecules called "short hairpin RNA" (shRNA), designed against the thousands of HIV variants known to currently exist. shRNA harnesses RNAi such that individual genes can be highly specifically "turned off" at will. It has been known for some time that single shRNAs can attach to the genetic material of HIV and silence the production of certain gene products.

Unfortunately like traditional drugs, the effect of a single shRNA is short-lived as HIV rapidly mutates to escape RNA interference. Using a cocktail of [about] 4 different shRNAs at the same time however, significantly reduces the virus’ ability to mutate and escape the genetic attack. By studying thousands of different combinations of shRNAs, the team has identified several combinations to cover all variants commonly found in the USA and Europe.

Principal investigator Glen McIntyre said, "The difficulty in finding a single combination of shRNAs to fight HIV is that there are many different variants that have to be accounted for. The trick is to search for combinations of slightly more shRNAs (than minimally needed for a single variant) so that there will be at least one suitable sub-combination for each different variant likely encountered. Not only did we
want our combinations (of shRNA) to cover all currently known subtype variants, but we also aimed for them to actively prevent the emergence of any new, resistant variants."

The team's persistence has paid off and they have created a number of combinations of just 6-7 shRNAs designed to suppress every single variant of HIV belonging to the Clade B subtype; the most common group found in the USA and Europe. "The goal now is to test the best combinations in long-term experiments against different variants to see if they hold up as expected, and particularly in preventing new variants from emerging." Success could one day see an entirely new treatment method for HIV suffers, potentially free of the problems associated with traditional drugs. 1/14/11

Reference

Small Difference in Physical Function between Older HIV Positive and Negative People

**SUMMARY:** Aging HIV positive U.S. veterans had slightly but significantly worse physical function than their HIV negative counterparts, and experienced greater yearly declines, according to study findings reported in the January 2011 issue of AIDS Patient Care and STDS. Differences diminished, however, after controlling for confounding factors such as injection drug use and hepatitis C coinfection, and when comparing people with specific diseases.

By Liz Highleyman

As people with HIV live longer thanks to effective antiretroviral therapy, aging has become a key focus of HIV medicine. A growing body of evidence indicates that HIV positive people have a higher risk of progressive age-related conditions such as cardiovascular disease, osteoporosis, and neurocognitive impairment—and tend to develop them at younger ages—but the relation between HIV and physical function has not been extensively studied.

To investigate this issue, Krisann Oursler from the University of Maryland School of Medicine and colleagues performed a cross-sectional analysis of physical function in 3227 HIV positive and 3240 HIV negative participants enrolled in the Veterans Aging Cohort Study (VACS-8) during 2002-2006. Most were men and the average age was about 50 years. Poor health predictors (such as smoking and heavy alcohol use) and comorbid conditions were common in both groups.

The researchers asked about areas of physical function ranging from basic activities of daily living (feeding, bathing, dressing) to instrumental activities of daily living (light, moderate, and heavy work), mobility (walking a few steps, walking inside, walking 1 block), and vigorous activity (walking uphill, running, sports). Participants report their current ability to perform each activity. Self-reported physical function correlated with results on a standardized test, the Short Form-12 physical subscale.

**Results**

- Overall, better physical function predicted longer survival.
- Across all age groups, decline in physical function per year was greater for HIV positive compared with HIV negative participants—a small but statistically significant difference.
- The physical function of the average 50-year old HIV positive patient was equivalent to that of the average 51.5-year-old HIV negative participant.
- When stratifying by age, however, HIV positive people in the youngest group (< 44 years) had better function than HIV negatives, while in the oldest group (> 55 years) they had worse function.
- HIV positive people were more likely than HIV negative participants to have certain cofactors for decreased physical function, including injection drug use (34% vs 16%, respectively) and hepatitis C (31% vs 15%, respectively).
- After controlling for confounding factors, HIV itself was no longer significantly associated with poorer physical function.
- History of cardiovascular disease was a significant predictor of poorer function, with a similar effect in the HIV positive and negative groups.
- Among people with chronic pulmonary disease, HIV positive patients fared worse, however, with a 50-year old having physical function equivalent to that of a 68.1-year-old...
HIV negative person.

Based on these findings, the study authors wrote, "We conclude that age-associated comorbidity affects physical function in HIV-infected patients, and may modify the effect of aging."

"Longitudinal [following over time] research with markers of disease severity is needed to investigate loss of physical function with aging, and to develop age-specific HIV care guidelines," they added.

"Within the limits of a cross-sectional study, the difference in function between younger and older patients was greater in HIV-infected patients compared to the uninfected patients, adjusted for comorbidity," they elaborated in their discussion.

"It should be noted in the younger (age ≤ 44 years) age group that HIV-infected patients reported higher function than uninfected patients," they continued. "Only this age group of HIV-infected patients had similar frequency of exercise compared to the uninfected patients. This finding raises the question of the role of physical inactivity in worse physical function among older HIV-infected patients."

Reference


New Light Shed on River Blindness Parasite

ScienceDaily (Jan. 12, 2011) — The team found that a bacterium inside the worm acts as a ‘disguise’ for the parasite, resulting in the immune system reacting to it in an ineffective way. The bacteria protect the worm from the body’s natural defences, but once the bacteria are removed with antibiotics, the immune system responds appropriately, releasing cells, called eosinophils, that kill the worm.

Antibiotics are successful against the parasite, but the long treatment regime means that it has limited use across whole communities. These new findings suggest that if medics could prime the immune system to recognise the worm, a shorter duration of antibiotic treatment may be sufficient to overcome its bacterial defences.

River blindness is caused by black flies that breed in rivers and deposit the larvae of a worm into the person they bite. The infection leads to severe itching of the skin and lesions of the eye which can result in blindness. It affects millions of people in developing countries, particularly in West and Central Africa. A closely related parasite also infects cattle, which causes lumps to appear on the animal's skin but does not cause blindness or other illness.

Dr Ben Makepeace, from the University’s Institute of Infection and Global Health, explains: "Our team has already shown that removing the bacteria with antibiotics results in the death of the worm, but until now we were unaware of how the bacteria protected the parasite in the first instance. Antibiotics can rid the parasite of the bacteria, allowing the immune system to respond properly, but it is a long treatment process, lasting up to six weeks.

"Now we can begin to look for a way to ‘prime’ the body into reacting to the parasite more efficiently. Currently there is no vaccine for river blindness, but if a candidate could be identified this may help boost the immune system ahead of antibiotic treatment and reduce the length of time patients have to take the drug. It is essential that whole communities are cured of the infection and the more we know about the mechanisms the parasite uses to survive in the body, the further we can progress with finding a practical treatment that kills adults worms and not just the larval stages."

Journal Reference:


Early Development of Anti-HIV Neutralizing Antibodies

ScienceDaily (Jan. 14, 2011) — New findings are bringing scientists closer to an effective HIV vaccine. Researchers from Seattle Biomedical Research Institute (Seattle BioMed), Vanderbilt University and the Ragon Institute of MGH, MIT and Harvard report findings showing new evidence about broadly-reactive neutralizing antibodies, which block HIV infection. Details are published January 13 in the open-access journal PLoS Pathogens.

According to author Leo Stamatatos, Ph.D., director of the Viral Vaccines Program at Seattle BioMed and a major stumbling block in the development of an effective vaccine against HIV is the inability to elicit, by immunization, broadly reactive neutralizing antibodies (NAbS). These antibodies bind to the surface of HIV and prevent it from attaching itself to a cell and infecting it. However, a fraction of people infected with HIV develop broadly neutralizing antibodies (bNAbS) capable of preventing cell-infection by diverse HIV isolates, which are the type of antibodies researchers wish to elicit by vaccination.
"We've found that the people who develop broadly-reactive neutralizing antibodies—which are about 30% of those infected—tend to have a healthier immune system that differs from others who don't develop those antibodies," Stamatatos explained, saying that these antibodies target only a few regions of HIV which is good from the standpoint of vaccine development. "It gives us less to target," he said.

In addition, the new findings show that these antibodies are generated much sooner than previously thought, in some cases as soon as a year after infection.

"These studies provide a strong rationale to begin teasing out the early immunological signals that allow some individuals, but not others, to mount broadly reactive neutralizing antibody responses," adds co-author Galit Alter, Ph.D.

"Now we know that these broadly-reactive neutralizing antibodies don't develop simply by chance and we can work to understand what makes this 30% of the HIV-infected population different," Stamatatos explained. By understanding that, we can hopefully use that information to design new immunogens and immunization protocols that can mimic the early events that lead to the development of such antibodies during natural infection."

**Journal Reference:**

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**Accelerated ageing of the immune system linked to heart disease risk in women with HIV**

Keith Alcorn
Published: 17 January 2011

Accelerated ageing of the immune system, caused by chronic HIV infection, was strongly associated with harmful changes in the carotid artery that may lead to long-term cardiovascular disease in women with HIV, US researchers report in an article published in advance online by the *Journal of Infectious Diseases*.

People with HIV infection appear to have an elevated risk of cardiovascular disease such as heart attack and stroke. People with HIV also have a high frequency of subclinical signs of progressive cardiovascular disease, or atherosclerosis, such as greater deposition of cholesterol and other debris on the walls of arteries (plaques), and thickening of the walls of the carotid artery.

In part these changes are due to lifestyle factors such as smoking, which is more common in people with HIV, and raised cholesterol levels caused by some antiretroviral drugs.

However there is growing concern that even in the absence of multiple risk factors, long-term infection with HIV may directly increase the risk of heart disease by promoting a permanent inflammatory state. Chronic viral infections can also cause accelerated ageing of the immune system, which may damage blood vessels in ways that promote the development of heart disease.

Dr Robert Kaplan of Einstein College of Medicine, New York, led a study to investigate the effect of accelerated ageing of the immune system on the cardiovascular health of women with HIV infection.

Ageing of the immune system (immunosenescence) is characterised by a decline in the number of new naïve T cells manufactured, a loss of memory T cells programmed to respond to specific infections, less aggressive proliferation of T cells in response to infections and higher levels of some inflammatory cytokines. All these defects explain why older people may be prone to more infections, and to suffer more ill health when they do acquire an infection.

These traits of an ageing immune system are usually seen in the elderly, and have been linked to heart disease. This study set out to determine if immunosenescence can also be found in younger people with HIV infection, and the extent to which it predicted cardiovascular disease.

The study compared measures of carotid artery disease and T-cell activation and immunosenescence in 115 HIV-infected women and 43 HIV negative women matched by age and ethnicity. All were participants in the Women’s Interagency HIV Study, a prospective study that included carotid artery ultrasound scans in its investigations.

The investigators measured T-cell activation by looking at levels of co-expression of CD38 and HLA-DR markers on CD4 and CD8+ T cells, and senescence by looking at the absence of CD28 and presence of CD57 markers.

They found significantly higher frequencies of activated CD4+ and CD8+ T cells, and of senescent CD8+ T cells, in HIV-positive women. Activation was lower, but not absent, in women on fully
suppressive antiretroviral therapy, indicating that even very low levels of HIV continue to cause immune dysregulation.

The level of activation in women with HIV was associated with the extent of carotid artery lesions, after controlling for age, CD4 count, viral load and antiretroviral therapy. Activation in women without HIV was lower and not associated with carotid artery lesions, suggesting either an effect of HIV or concurrent pathogens such as CMV or hepatitis C on the vascular wall, or the existence of a threshold of immune activation that is necessary before it affects the vascular wall.

A higher level of CD8+ T cell senescence was significantly associated with carotid artery lesions in HIV-positive women, but not in HIV-negative women (p=0.009). This was not reversed by antiretroviral therapy.

The study is limited by its cross-sectional design which relied on measurements and blood samples taken at one visit in women, and prospective data are needed to further understand the links between immune activation, immunosenescence and cardiovascular disease in people with HIV.

In an accompanying commentary Virginia Triant and Steven Grinspoon of Massachusetts General Hospital say that long-term follow-up is needed to better understand the association seen in this study, with further investigations required to see whether the same phenomenon is found in men.

They also note that if the association holds in future studies, attempts to treat immune senescence through immunosuppressive drugs, cytokine inhibitors or telomere-based therapies “will need to be balanced against potential negative immunological effects. Indeed this balance may be difficult to achieve.”

References
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2. Trant VA, Grinspoon SK. Immune dysregulation and vascular risk in HIV-infected patients: implications for clinical care. J Infect Dis, advance online publication, January 10th, 2010, Click here for free access to an extract from this article.

AIDS is a plague allowed to happen ****

By Larry Kramer, Special to CNN
January 14, 2011—Updated 1820 GMT (0220 HKT)

New York City (CNN)—I want this article to break your heart. But it deals with a subject that has had a tough time of it in the break—everyone’s-heart department. I’ll bet that a number of you will be more angry at me than sympathetic by the time you finish reading it. If indeed you finish reading it.

From its very beginning, most people have not wanted to know the truths about AIDS. This is an indisputable fact that continues until this very minute. I have been on the front lines since Day 1, so I know what I’m talking about.

Here are 10 realities about AIDS, and I’ve learned them the hard way:
1. AIDS is a plague—numerically, statistically and by any definition known to modern public health—though no one in authority has the guts to call it one.
2. Too many people hate the people that AIDS most affects, gay people and people of color. I do not mean dislike, or feel uncomfortable with. I mean hate. Downright hate. Down and dirty hate.
3. Likewise, both people who don’t have sex the way they do (if they have it at all) and people who take drugs in order to feel better in a world that they find wretched are considered two highly expendable populations by the powerful forces that control this world.
4. AIDS was allowed to happen. It is a plague that need not have happened. It is a plague that could have been contained from the very beginning.
5. It is a plague that is not going to go away. It is only going to get worse.
6. There is no cure and the amount of money expended toward finding one is pathetically small, miniscule, puny, and totally indicative of a system and a government and a country and a world that does not want to end this plague.
7. There is no incentive for pharmaceutical companies to find a cure since they are making billions selling, at highly inflated prices, the many anti-viral drugs that those infected must consume—drugs that only keep us living but still infected just enough to continue to possibly still infect others.
8. Educational campaigns, indeed all attempts at prevention, have been too stupid, useless, lily-livered, and nicey-nicey to accomplish much of anything.
9. There is no one of any use really in charge of this plague, in America or anywhere else in the world—and it is a worldwide plague by now—and this lack of decent, responsible and humane
leaders has been so since its beginning in 1981. They lie to us. I consider most of those who have been or are in charge as equal to murderers.

10. One out of every five men who have sex with men in America is now HIV-positive, and more than 50% of gay men do not know it. Doctors in Chelsea say the statistics for that New York neighborhood have jumped from one out of five to one out of four. At the rate things are going, almost all gay men in America could be HIV-positive, which a lot of people would really like to see happen.

These are appalling statistics, appalling statements, appalling facts, and yet no one responds to them when I raise them. Why should they? Too many people want too many other people dead, and it is fearful and as we continue to see over and over, often dangerous to confront them.

30 years of HIV—Three men reflect

Governments and bureaucrats and presidents and politicians and the people who run this world lie to people. They tell us HIV is under control. They tell us case numbers are decreasing. They tell us that all is being done that can be done. They tell us HIV is too complicated to eradicate. They tell us gay people and people of color have made more progress than ever before. These are all lies.

We must not believe them. How could we when, in one place or another:

- They also tell us we can't get legally married.
- They also tell us that we cannot legally adopt children.
- They also tell us religions will not recognize us.
- They also tell us we can't serve our country yet.
- They also tell us our real history cannot be taught in schools.
- They also tell us that gay students cannot organize in schools.
- They also tell us that people who murder us are not committing hate crimes.
- They also tell us we cannot insure our partners.
- They also tell us our partners are not legal.
- They also tell us we cannot have equal opportunities.
- They also tell us we can't kiss each other or hold each other’s hands in public.
- They also tell us that our Supreme Court doesn't want to know about any of this, doesn't want to make us free and equal, doesn't want to honor the Bill of Rights.

If you want to know why AIDS is a plague, I have just told you why.

I could add a thousand more "they also's." I could expound and expand and add so many facts and figures to the above they'd put you to sleep. I helped start the two major AIDS organizations in America. I have watched almost everyone I once knew die.

For some 30-plus years, I have been trying to tell the world where this plague came from and why, and I will continue to do so until I die, too.

You see, I simply can't get the memories and the ghosts of just about every friend I had out of my life. And since there is no doubt in my mind that this plague of HIV/AIDS that took them from me was and continues to be allowed to happen, I am duty bound to tell this hideous history as best and as fully as I can. It's the least I can do.

That is correct: This plague of HIV/AIDS was intentionally allowed to happen. It still is. Nothing has changed in the intentionality department. Hate has a way of hanging around forever and too often winning out in the end.

NYTimes, January 14, 2011

Behavior: They Report Abstinence, but S.T.D. Says Otherwise

By NICHOLAS BAKALAR

About 10 percent of young adults in a large study who tested positive for a sexually transmitted disease reported that they had been abstinent for the past year, and half of those said they had never had sex at all.

Researchers writing in the January issue of Pediatrics used a nationally representative sample of 14,012 students initially recruited in 1994. The students gave urine samples and filled out sexual behavior questionnaires. The researchers interviewed and retested the subjects in 2001 and 2002.

The average age of the subjects, about half of them women, was 22. Those who reported sexual activity were only twice as likely to be infected as those who reported none, a very small difference under the circumstances.
There were no significant differences in age, sex, race or education level among those who were infected but reported abstinence.

Jessica McDermott Sales, an assistant professor of public health at Emory University and one of the study’s authors, said that dishonesty was only one possible explanation for the discrepancy. But she added, “This is a fairly sizable portion of kids who are saying they’re not sexually active when they apparently are.”

The study also found that positive tests were about a third more likely in women than men, six times as likely in African-Americans as in whites, and a third more likely in those without a high school diploma than in high school graduates.

'Master Switch' for Key Immune Cells in Inflammatory Diseases Discovered

ScienceDaily (Jan. 17, 2011) — Scientists have identified a protein that acts as a "master switch" in certain white blood cells, determining whether they promote or inhibit inflammation. The study, published in the journal Nature Immunology, could help researchers look for new treatments for diseases such as rheumatoid arthritis that involve excessive inflammation.

Inflammatory responses are an important defence that the body uses against harmful stimuli such as infections or tissue damage, but in many conditions, excessive inflammation can itself harm the body. In rheumatoid arthritis, the joints become swollen and painful, but the reasons why this happens are not well understood.

Cells of the immune system called macrophages can either stimulate inflammation or suppress it by releasing chemical signals that alter the behaviour of other cells. The new study, by scientists from Imperial College London, has shown that a protein called IRF5 acts as a molecular switch that controls whether macrophages promote or inhibit inflammation.

The results suggest that blocking the production of IRF5 in macrophages might be an effective way of treating a wide range of autoimmune diseases, such as rheumatoid arthritis, inflammatory bowel disease, lupus, and multiple sclerosis. In addition, boosting IRF5 levels might help to treat people whose immune systems are compromised.

Researchers from Imperial College London previously developed anti-TNF treatments, a class of drug that is widely used as a treatment for rheumatoid arthritis. The drugs target TNF, an important signalling chemical released by immune cells to stimulate inflammatory responses. However, about 30 per cent of patients don’t respond to anti-TNF drugs, so there is a serious need to develop more widely effective therapies.

Dr Irina Udalova from the Kennedy Institute of Rheumatology at Imperial College London, the senior researcher on the study, said:

"Diseases can affect which genes are switched on and off in particular types of cells. Understanding how this switching is regulated is crucial for designing targeted strategies to suppress unwanted cell responses.

"Our results show that IRF5 is the master switch in a key set of immune cells, which determines the profile of genes that get turned on in those cells. This is really exciting because it means that if we can design molecules that interfere with IRF5 function, it could give us new anti-inflammatory treatments for a wide variety of conditions."

Gene association studies have linked variations in the gene that encodes IRF5 with an increased risk of autoimmune diseases. This led Dr Udalova and a PhD student in her lab, Mr Thomas Krausgruber, to investigate what role the protein plays in controlling inflammation.

They used engineered viruses to introduce extra copies of the IRF5 gene in human macrophages grown in the laboratory, making the cells produce more IRF5. When they did this to macrophages with anti-inflammatory characteristics, it made them switch to promoting inflammation. When they blocked IRF5 in pro-inflammatory macrophages using synthetic molecules, this reduced the cells’ production of signals that promote inflammation. The researchers also studied genetically modified mice that were unable to produce IRF5. These mice produced lower levels of chemical signals that stimulate inflammation.

IRF5 seems to work by switching on genes that stimulate inflammatory responses and dampening genes that inhibit them. It can either do this by interacting with DNA directly, or by interacting with other proteins that themselves control which genes are switched on. Dr Udalova's group are now studying how IRF5 works at a molecular level and which other proteins it interacts with so that they can design ways to block its effects.
Journal Reference:

By L. Caetano M. Antunes, Julian E. Davies and B. Brett Finlay

**Mining Bacterial Small Molecules**

As much as rainforests or deep-sea vents, the human gut holds rich stores of microbial chemicals that should be mined for their pharmacological potential.

Companies spend huge resources going to the far reaches of the Earth to search for the next blockbuster. But we need look no further than our own intestines, which are populated with thousands of bacterial species that are constantly producing and releasing small, bioactive molecules.

Small molecules—the bread and butter of pharmaceutical companies—are compounds of low molecular weight (under 3,000 daltons) and diverse chemical composition. Examples of such molecules are the steroid and small-peptide hormones of higher organisms, with a molecular weight around 300 daltons, which have many important biological functions. The term hormone (from the Greek: excite, arouse) was coined in 1905 by British physiologist Ernest Starling to describe the chemical messengers produced in an organ or gland of the body that travel to distant organs to exert their physiological effects. In humans, the critical functions of small-molecule hormones include modulation of the immune system, the development of sexual characteristics, the response to stress, metabolism, and mineral balance, among others.

Although much of our knowledge about bioactive small molecules comes from the study of mammalian and plant hormones, it is now known that bacteria can also produce, sense, and respond to a variety of small-molecule signals that enable them to act coordinately. Through the research of Alexander Tomasz on the acquisition and incorporation of foreign DNA by *Streptococcus pneumoniae* and Woodland Hastings’ studies of *Vibrio fischeri* luminescence, science had its first hints that diffusible molecules played an important role in the lifestyle of microbes. Decades of subsequent research revealed that these hormone-like compounds are produced by these bacteria at basal levels and accumulate as their numbers increase. Both Tomasz’s and Hastings’ groups noticed that after reaching a threshold concentration, these molecules could regulate the incorporation of exogenous DNA and the production of light, activities that are only useful when undertaken by a population. (Bacteria can take up DNA individually, but when it is taken up by a group, the community can increase its chances of survival due to its greater genetic diversity.) Although the consequences of such discoveries were not fully appreciated at the time—it was unclear whether this behavior would be found in all bacteria—the observations formed the foundation for studies of bacterial communication. It is now widely accepted that many bacterial species use small chemical compounds to communicate with others of the same species, other bacterial species, and their hosts. Because this phenomenon is dependent upon a threshold cell density, bacterial communication has been termed “quorum sensing.”

**Intestinal molecular signaling**

Microbes, both good and bad, can exert direct effects on host cells and vice versa. For example, pathogenic bacteria such as some strains of *E. coli* and *Salmonella* reduce the overall number of normal gut commensal bacteria, promoting their own growth, whereas some commensals have been shown to prevent pathogens from producing deadly Shiga toxin (A). Commensals also have essential chemical exchanges with the host. Gut bacteria are required for the normal development of the immune system, and the host actively dampens its normal immune response to allow commensals to grow (B). Pathogenic bacteria also affect the host cells directly, releasing signals that compromise the host immunity; indeed, some host signals, such as stress hormones, can exacerbate disease by increasing bacterial virulence (C).

Because of their specific actions, these channels of chemical communication can be a valuable reservoir to
tap for potential drugs. Like hormones, some these molecules could have downstream effects on distant organs like the pancreas, the lungs, or the brain. These channels of chemical communication can be a valuable reservoir to tap for potential drugs.

The chemical repertoire used by bacteria to communicate is diverse, and new bioactive molecules continue to be discovered. Nonetheless, our knowledge of these molecules is limited. Studies of bacterial signaling have focused mostly on laboratory-grown, pure cultures of microorganisms. In the natural environment and in their hosts, microbes live in association with a multitude of other species and are constantly presented with opportunities for competition and cooperation.

One of the best-known natural examples is the nitrogen-fixation–driven symbiosis between *Rhizobia* and their legume hosts. Many chemical signals act to promote the establishment of this mutually beneficial relationship. For example, the growing root exudes flavonoids, which induce the surrounding *Rhizobia* to migrate to the root surface. There, quorum sensing occurs through the production of acylhomoserine lactones, culminating in the production of microbial nodulation factors that act on the root and finally result in an endosymbiotic relationship. Although there is a wealth of information about chemical signaling in soil, many other complex microbial populations exist in nature, and it is certain that microbial signaling plays important roles in these communities.

At elevated concentrations, microbial signals can act as antimicrobials. In general, however, microbes produce antibiotics in the environment at concentrations that do not affect their growth.\(^5\) It is probable, then, that the main function of these chemicals is to modulate bacterial gene expression rather than to poison.\(^6\) Nevertheless, the study of chemicals derived from microbes and other organisms has provided us with more than just information about the roles that small molecules play in biological systems. Whenever possible, humans have taken advantage of these natural products for therapeutic purposes, the classic example being the fortuitous discovery of the antibiotic penicillin. In addition to antibiotics, natural products have been used as anticancer and anti-inflammatory compounds.\(^2\) Many have been isolated from microorganisms, but others have been derived from plants and marine life. The discovery that the human body is made up of extremely complex ecosystems suggests that it, too, could be used as a rich source of new bioactive molecules.

**The wealth within**

At birth, humans are colonized by complex communities of microbes. These communities, which are established within the first year of life, have been termed microbiota, microflora or microbiome. The human microbiome is extremely rich, containing upwards of \(10^{14}\) cells,\(^9\) and is essential to our health. Microbes colonize our skin, our gastrointestinal (GI), genitourinary, and respiratory tracts. Researchers have estimated that the collection of microbial genes in our bodies exceeds our own genes by a factor of \(100\), which means that the human genome is predominantly prokaryotic.

It is probable, then, that the main function of these chemicals is to modulate bacterial gene expression rather than to poison.

Although virtually every body surface that is exposed to the environment harbors microbes, the gastrointestinal tract is by far the most heavily colonized site. More than 1,100 bacterial species have been genetically identified in the human gut; each individual carries an estimated 160 distinct species, only about one-tenth of which appear to be shared by everyone.\(^9\)\(^,\)\(^10\) This offers a tremendous opportunity for the evolution of multiple microbe-microbe and host-microbe interactions, many of which are conveyed through the activity of small signaling molecules.

It has been known for a while that commensal organisms can use diffusible signals to interact with their hosts. *Bacteroides thetaiotaomicron*, a prominent member of the human gastrointestinal microbiota, produces signals that can control host gene expression. By doing so, the bacterium controls the availability of nutrients in its surroundings to favor its growth. More recently, this intestinal commensal has also been shown to communicate with pathogens by producing a yet to be identified signal that can control virulence-factor production by enterohemorrhagic *Escherichia coli*, a pathogenic strain of *E. coli* that can cause serious illness and death in humans. Colonization by *B. thetaiotaomicron*, and possibly by other bacterial species, may be an important tool used by mammals to control infection by virulent bacteria.

These interactions are not always initiated by the microbiota. Host-produced small molecules can also have profound effects on both commensals and pathogens. The mammalian stress hormones epinephrine and norepinephrine have been shown to affect commensal microbial populations in the gastrointestinal tract. Although the mechanism involved is not known, these hormones can favor the growth of specific species of the human microbiome. In addition to their roles in normal physiology, these mammalian stress hormones can also influence the production of virulence factors by invading pathogens. For
instance, upon sensing intestinal epinephrine and norepinephrine, enterohemorrhagic E. coli activates the production of its type III secretion system, a major virulence factor. Also, Campylobacter jejuni, which commonly causes food poisoning, can respond to norepinephrine by improving its ability to enter host cells.

An even more daring possibility is that some of these molecules could be used to manipulate the physiology of remote organs and systems. Although data on the importance of the human microbiome to health has been accumulating over the past few years, new evidence suggests that its contributions are not always local. The microbiota exerts an impact on host tissues and organs far away from the gut. Changes in intestinal commensal populations have been correlated with many diseases of remote organs, such as diabetes, asthma, obesity, cancer, autism, and even depression. The fact that these organs are not in direct contact with gut commensals suggests that chemical signals may be involved. For instance, it has been known for a while that antibiotic usage is correlated with an increased risk of allergic diseases, and it has been suggested that this is due to effects on the intestinal microbiota. Although microbial interactions with the human immune system are crucial in producing these pathologies, it is also possible that the intestinal microbiota affect systemic metabolites by a more general mechanism. Indeed, William Wikoff of the Scripps Research Institute and colleagues have recently shown that intestinal microbes can have a significant impact on mammalian blood metabolites, particularly those involved in amino acid metabolism, suggesting that the influence of gut microbes on the human body may be largely dependent on the activities of small molecules. Although some of these effects may be brought about directly by microbial signals, other mechanisms that propagate messages initiated by gut bacteria may also be at play.

The mammalian gut plays an important role in the excretion of waste, and many host-produced small-molecule metabolites that circulate in the gut are a result of this waste-production process. The GI tract is also loaded with other small molecules, such as hormones and bile acids, that not only have significant impact on the GI tract itself but also on other organs through reabsorption. In other words, the molecules with potential bioactivity may not necessarily come only from the microbiota, but also from our own waste products.

Some of these small molecules originating from the host and from the microbes are also likely to have important functions in keeping the relationship between hosts and their commensals in balance. Since these molecules have important functions in human health and disease, they could be mined as therapeutics aimed at maintaining or reestablishing homeostasis and preventing or curing diseases. Not least, the gut may be a source of new antibiotics. It is known that the microbiota exerts important effects on the maturation of the mammalian immune system, and the small molecules in the intestine could be used to modulate these relationships in controlled ways. An even more daring possibility is that some of these molecules could be used to manipulate the physiology of remote organs and systems. It is possible that the molecules produced by some of the microbes associated with protection against certain diseases could be used to remediate or prevent those illnesses. While the potential for applications is enticing, careful studies must be designed and performed to demonstrate that changes in bacterial populations and the molecules they produce during disease are in fact causing the pathological process rather than changing in response to it.

**Stalling between discovery and drug development**

One of the limitations of this potential source of bioactive small molecules is that, like bacteria isolated from deep-sea vents and other exotic locales, the majority of the microbial species present in the mammalian gut still cannot be cultured in the laboratory. Working out a bacterium’s ideal growth requirements is no simple matter. This has forced the use of culture-independent methods to study microbial communities in and on humans.

Most studies rely on metagenomics, or the unbiased sequencing of DNA fragments isolated from mixed microbial populations. This is useful from a phylogenetic standpoint because it allows us to determine the exact microbial composition of a given sample, but it tells us very little about functions of the compounds produced or the interactions between them. Based on analysis of the gut metagenome—the combination of all genes present in the GI tract—we can predict that many biological reactions are yet to be discovered. More recently, the intestinal environment has been studied using other culture-independent methods such as metatranscriptomics and metaproteomics, which focus on the unbiased analysis of messenger RNA or proteins, respectively. Altogether, these explorations of the microbial diversity in the GI tract suggest that significant phylogenetic diversity remains to be explored. These studies have provided much information about the composition of microbial communities in the
mammalian gut, but it is only recently that we have begun to decipher the molecular functions of these assemblages.

With the overwhelming amount of genetic material present in the human gut comes the potential for an immensurable source of bioactive small molecules. As a result of recent advances in techniques of chemical separation and structural elucidation, particularly methods for high-throughput analysis of complex samples, we now have tools to probe this chemical lexicon. One such technique is Fourier Transform Ion Cyclotron Resonance Mass Spectrometry (FTICR-MS), which has recently been used in pioneering high-throughput studies of the mammalian metabolome. FTICR-MS is an extremely sensitive and accurate method for the rapid detection and relative quantification of thousands of small molecules in complex samples. We have used FTICR-MS to study the intestinal metabolome and find that thousands of small molecules are present in the mammalian gut. Interestingly, the levels of the majority of these molecules are affected by antibiotic treatment, suggesting that the intestinal microbiota modulates the chemical composition of the intestinal lumen (Antunes and Finlay, submitted for publication). Additional metabolic studies of samples from healthy and disturbed ecosystems will allow predictions of causative associations between chemical variations and specific disease states.

But even these “OMIC” studies, informative as they may be, will need to be verified and tested in basic laboratory experiments to tease apart the specific host-microbe interactions. There is a huge distance between beholding the vast landscape of molecules with potential human applications and finding potential disease interventions. The results from survey studies will need to be used to develop hypotheses that can then be tested using single molecules (natural or synthetic) to treat conditions in animal models, giving us insight not only into the healthy state, but also into how it can be maintained or restored during disease.

That DNA, RNA, and proteins are central to life is irrefutable. However, the functioning of living organisms not only depends on these molecules but, in most cases, extends to incorporate the end products of multiple metabolic pathways. In other words, in most cases it is the small molecules that are the crux of biological function. While other sources of bioactive molecules should not be ignored, harnessing the bacterial chemicals in our own gut may yield molecules that have already been shaped for very specific interactions through years of coevolution between humans and their microbial partners. Without identifying and studying these molecules, we will not fully understand the functions of metabolic pathways and the interconnections among them. Nor will we be able to fully comprehend the complexities of any biological system. The study of small molecules should be undertaken not only with an intellectual view toward understanding the molecular intricacies of life in more detail, but also with a practical view of benefitting from what these molecules may have to offer.

L. Caetano M. Antunes, F1000 Head of Faculty Julian E. Davies, and Section Head B. Brett Finlay are at the University of British Columbia, Vancouver, BC, Canada.

References:
By Jef Akst

**New gut bacteria regulate immunity****

Another example of commensal microbes that affect host immunity may hold implications for the treatment of autoimmune diseases and other ailments

[Published 23rd December 2010 07:00 PM GMT]

An abundant type of bacteria that resides in the intestines is critical for keeping the immune system of the colon in check, according to a study published online today (December 23) in *Science Express*.

The results add to the growing body of literature that commensal microbes in the gut are key regulators of host immunity, and may provide potential therapeutic avenues for inflammatory bowel disease (IBD), allergies, and autoimmune diseases.

"This is a big step forward in understanding how the commensal microbiota shapes the host immune system," immunologist Paul Forsythe of McMaster University in Ontario, who was not involved in the study, told *The Scientist* in an email. "These results suggest that not only are there specific immune responses to distinct bacterial species, but that these responses are region-specific within the intestine."

Over the past several years, evidence has been accumulating that the gut microbiome affects the balanced host immune system. Segmented filamentous bacteria (SFB), for example, appear to induce the production of intestinal Th17 cells, helper T cells that are critical to fighting pathogens.

Too many Th17 cells, however, can promote autoimmunity without the proper balance of regulatory T cells (Tregs) to suppress the immune response against one's own cells. To see whether certain commensal bacterial species might regulate the production of Tregs in the intestines, immunologist Kenya Honda of the University of Tokyo and his colleagues compared normal mice to germ-free mice that harbored no bacteria. They found no major differences in the small intestine, but significantly fewer Tregs in the colon, suggesting that the missing bacteria may be inducing Treg production.

Antibiotic and chloroform-based tests revealed that the responsible microbes were likely spore-forming, Gram-positive bacteria. As *Clostridia* are one of the most abundant gut bacteria that fit this description, Honda and his colleagues colonized germ-free mice with a cocktail of 46 different strains of *Clostridia*. The results confirmed their suspicion—the bacterial treatment resulted in the accumulation of Tregs in the colon. Treg levels in the small intestine did not change, however, suggesting that *Clostridia* only affect the production of Tregs in the lower part of the digestive tract.

"This is one of the first studies that identifies a specific example of a commensal microbe affecting regulatory T cells," said coauthor Ivaylo Ivanov, an immunologist at the Columbia University Medical Center in New York. There was a study published earlier this year, he noted, that suggested another bacteria, *Bacteroides fragilis*, could also induce Treg production in the gut, but those researchers "saw a very marginal induction of regulatory T cells," said Ivanov, who collaborated on the research while at New York University School of Medicine. "This study identifies *Clostridia* as a really strong inducer."

If these results are representative of the human microbiome's effects on immunity, researchers might one day be able to manipulate the gut microbiota for therapeutic purposes, Forsythe added.

Certain species of *Clostridium* are less abundant in IBD patients than healthy controls, for example, suggesting a role for the bacteria in healthy digestion. Furthermore, "your Treg response has been shown to be very important in allergy and asthma and a lot of chronic disease states, so it could be critically important that you have enough of these organisms and others to maintain this proper microbial balance, which then contributes to a proper immunological balance," said immunologist Liam O'Mahony of the Swiss Institute of Allergy and Asthma Research, who did not participate in the research.

"I think if we can determine how these bacteria mediate their immune effects, this may open the door to new therapeutic strategies for IBD and perhaps other disorders including allergic disease," Forsythe agreed.

Indeed, at least one clinical study published in 2005 has already demonstrated a therapeutic effect of an individual microbe, O'Mahony said. Symptoms of irritable bowel syndrome improved significantly...
when the patients received doses of live *Bifidobacterium infantis* cells for eight weeks, a change accompanied by normalization of the ratios of anti-inflammatory to proinflammatory cytokines.

The new study provides "tantalizing data that fits with this story," he said. "Some bugs are important for one type of immunity and other bugs are important for another type of immunity, and it's really the balance of these bugs that gives the perfect immune system."


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**the Bacteria use us, just as we use them**
by Steven Pace, [Comment posted 2011-01-07 03:42:22]

It is logical that bacteria would learn to manipulate our immune system so that we can destroy their competition for them. Some bacteria, especially gram-negative, have developed ways to cause us to weaken ourselves, so it is not all that surprising that the friendly bacteria do the same thing. You just can look at an animal like us, and understand, without understanding the gut bacteria, about 1,200 types, that live inside us. It is integral to our digestion, immune system, and all other systems as well.

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**Ironing Out Bacteria**
by Tom Hennessy, [Comment posted 2010-12-29 09:54:49]

This shows the bacteria are affected by iron therefore giving credence to the theory of iron fortification being THE cause of Irritable Bowel. Iron SPECIFICALLY allows for the growth of this bacteria. "The effects of iron fortification on the gut microbiota in African children: a randomized controlled trial in Cote d'Ivoire." "Anemic African children carry an unfavorable ratio of fecal enterobacteria to bifidobacteria and lactobacilli, which is increased by iron fortification. Thus, iron fortification in this population produces a potentially more pathogenic gut microbiota profile, and this profile is associated with increased gut inflammation." "Iron complexation was investigated as a possible tool to give lactobacilli a competitive advantage over clostridia. The iron complexing substance tested, i.e. 2,2'-dipyridyl, was not toxic itself for clostridia, but its addition to a mixed culture of lactobacilli and clostridia resulted in a strong ecological advantage of the lactobacilli."

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**Other bacteria do the same thing**
by anonymous poster, [Comment posted 2010-12-26 15:57:01]

It is good to know that there are *Clostridia* that can stimulate innate immunity. It would be nice if they would say in the story that this work has been going on for near a decade and that strains of *Bacteroidetes* were identified a few years ago as inducing the same cascade of effects. There are recent papers elaborating the phenomena and particularly by Lasker's group at Harvard. It is, however, an important area for continued research.

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**Surgeons spooked by—and overreacting to?—2007 HIV-positive organs incident**

In November 2007, four organ transplant recipients in Chicago contracted HIV and hepatitis C from a deceased "high risk" organ donor.

It was a nightmare scenario, to be sure, but it was also an extreme rarity: the first documented case of HIV transmission through an organ transplant in more than 20 years.

Still, the ripple effect for surgeons who perform organ transplants has been significant, according to a study published Monday in the journal *Archives of Surgery*. Nearly a third of 422 practicing transplant surgeons surveyed by a Johns Hopkins research team in early 2008 changed the way they evaluate organs from "high risk" donors as a result of the 2007 incident, they reported.

While it’s great that surgeons are aware of risks and take appropriate precautions, the researchers suggest, they might not be making changes to policy that help patients most. Rather, most of the adjustments made could have been considered "defensive medicine"—moves designed to protect the surgeon, who might fear getting sued, rather than transplant patients, who desperately need donor organs.
For example, 41.7% of the surgeons who said they changed their practices reported decreased use of high-risk donors. An additional 31.6% said that they ramped up their emphasis on informed consent—getting patients to assume responsibility for unlikely complications.

But different types of changes might have better served patients. In the 2007 case, the donor's antibodies tested negative for HIV and hepatitis C, but later nucleic acid testing was positive, which means that the donor may have died during what is called the "window period" between infection and detectability. Increased use of nucleic testing could have flagged the organs in time, making it unnecessary to turn away all organs from high-risk donors at a time when organs are in such short supply.

The Hopkins team wrote that the chance of getting HIV or hepatitis C from a high-risk organ is not much higher than the risk of acquiring either disease while awaiting transplant. More than 8% of organ donors are high-risk.

"Given the severity of the organ shortage and high incidence of waiting-list mortality, centers should strive for appropriate rather than decreased use of high risk donors," the team wrote.

**South Africa 'Whoonga' Is New Threat to HIV Patients**

*Reuters*, (01.13.2011)  Jon Herskovitz

South African HIV/AIDS experts and law enforcement personnel are closely monitoring “whoonga,” a street drug laced with crushed tablets of the HIV drug efavirenz, or Stocrin. Whoonga is a highly addictive marijuana [and possibly heroin] cocktail that can include rat poison and other cheap substances [such as detergent powder]. Police say boosting it with the HIV drug has little effect, but street users believe it amplifies whoonga's hallucinogenic properties.

"It is a relatively new drug that began to surface a few months ago and fortunately for now, is confined to a few new areas," said Vish Naidoo, a spokesperson for the national police agency. Antiretroviral (ARV)-laced doses of whoonga sell for $2-$3 a hit.

As the government continues efforts to make ARVs more widely available to the millions of HIV/AIDS patients who need them, authorities are cracking down on drug gangs, tightening security for ARV supplies, and alerting patients to the risk of theft. While officials believe they can contain whoonga's reach, some patients and clinics in towns in eastern KwaZulu-Natal already have been robbed of their ARVs.

Ntombizonke Ndlovu, a provincial official with the HIV/AIDS advocacy group Treatment Action Campaign, said "people as young as 13, 14, and 15" are "getting mixed up in this whoonga thing. Crime is growing like crazy."

Crime victims have mostly remained silent, fearing that by reporting thefts they will be exposed as being HIV-positive. Despite some 5.7 million people having HIV/AIDS in South Africa's population of 49 million, the disease remains heavily stigmatized.

**Reducing Drug Use, Human Immunodeficiency Virus Risk, and Recidivism Among Young Men Leaving Jail: Evaluation of the REAL MEN Re-Entry Program**

*Journal of Adolescent Health Vol. 47; No. 5: P. 448-455*, (11.2010)  Nicholas Freudenberg, DrPH; Megha Ramaswamy, PhD, MPH; Jessie Daniels, PhD; Martha Crum, PhD; Danielle C. Ompad, PhD; David Vlahov, PhD

The Returning Educated African-American and Latino Men to Enriched Neighborhoods (REAL MEN) intervention is designed to reduce drug use, risky sexual behavior, and criminal activity among males ages 16-18 leaving New York City jails. The current study assessed the impact of this multifaceted approach.

A total of 552 participants were recruited in city jails and randomly assigned to receive either an intensive 30-hour jail/community-based intervention or a single jail-based discharge planning session. In addition, all the men were referred to optional services at a community-based organization (CBO). One year after release from jail, 397 (72 percent) completed a follow-up interview. REAL MEN’s impact on drug use, risky sexual behavior, criminal justice involvement, and school/work involvement post-release was evaluated using logistic and ordinary least squares regression.

The results showed assignment to REAL MEN and, independently, use of CBO services, significantly reduced the odds of substance dependence (odds ratio=.52, p=.05; OR=.41, p=.05, respectively) one year post-release. Participants assigned to the intervention spent 29 fewer days in jail compared with those in the control group (p=.05). Compared to non-CBO visitors, those who visited the CBO were more likely to have attended school or found work in the year after release (OR=2.02, p=.01).
“Jail and community services reduced drug dependence one year after release and the number of days spent in jail after the index arrest,” the researchers concluded. “While these findings suggest that multifaceted interventions can improve outcomes for young men leaving jail, rates of drug use, risky sexual behavior, and recidivism remained high for all participants after release from jail, suggesting the need for additional policy and programmatic interventions.”

Genentech Warns of Infection Risk from Alcohol Pads Packaged with Fuzeon and Pegsys

SUMMARY: Genentech last week notified patients that alcohol pads packaged with certain injectable drugs—including the HIV entry inhibitor enfuvirtide (Fuzeon; T-20) and pegylated interferon alfa-2a (Pegasys) used to treat hepatitis B and C—may be contaminated with bacteria that could cause serious infection, especially in people with suppressed immune function. Triad Group, which manufactures the potentially contaminated alcohol pads and swabs, has announced a market recall. Genentech emphasized that only the alcohol products, not the medications themselves, are affected.

Below is the text of a recent Genentech advisory outlining the concerns.

Genentech Informs Customers of Important Information about Triad Group’s Alcohol Prep Pads

South San Francisco, Calif.—January 13, 2011—Genentech, Inc., a member of the Roche Group, has become aware of the market recall of Triad Group’s alcohol prep pads, alcohol swabs, and alcohol swabsticks manufactured by Triad in the United States and marketed under various brand names. The Triad Group alcohol prep pads are co-packaged and distributed with Genentech medicines Boniva Injection, Fuzeon, Nutropin A.Q. Pen, Pegasys, and TNKase to customers in the United States.

According to the Food and Drug Administration’s (FDA) Medwatch communication, the recall was initiated due to concerns about potential contamination of the Triad Group’s products with the bacteria, Bacillus cereus. This recall involves those products marked as sterile as well as non-sterile. Use of contaminated alcohol prep pads, alcohol swabs, and alcohol swabsticks could lead to life-threatening infections, especially in at-risk populations, including immune suppressed and surgical patients.

It is important to note, that Genentech medicines are not contaminated and may continue to be used in accordance with the package insert. Patients and healthcare providers should not use the alcohol prep pads packaged with these medicines and should instead use an alternate alcohol prep pad that is not involved with the Triad Group recall, or alternatively use a sterile gauze pad in conjunction with isopropyl alcohol for disinfecting the injection site prior to administration.

Genentech is in discussion with the FDA and is currently assessing alternatives to address the situation. The company plans to issue a Dear Healthcare Provider letter to potential prescribers and pharmacists to make them aware of the Triad product recall and the need to discontinue use of the alcohol prep pads packaged with Boniva Injection, Fuzeon, Nutropin A.Q. Pen, Pegasys, and TNKase.

Patients should consult their healthcare provider for further information. Healthcare providers with questions may contact the Patient Resource Center at 1-877-436-3683 between the hours of 6 a.m. and 5 p.m. Pacific Time.  1/18/11

- For the Boniva indication, full prescribing information, and important safety information, please visit www.boniva.com.
- For the Fuzeon indication, full prescribing information, and important safety information, please visit www.fuzeon.com.
- For the Nutropin A.Q. Pen indication, full prescribing information, and important safety information, please visit www.nutropin.com.
- For the Pegasys indication, full prescribing information, and important safety information including Boxed Warning and Medication Guide, please visit www.pegasys.com.
- For the TNKase indication, full prescribing information, and important safety information, please visit www.tnkase.com.
Triple ART Regimen Works Best to Prevent Mother-to-Child HIV Transmission

**SUMMARY:** An antiretroviral regimen containing 3 drugs reduces the risk of perinatal HIV infection during pregnancy, delivery, or breast-feeding more than using just 2 agents for prophylaxis, according to research in Africa published in the January 14, 2011, advance online edition of *Lancet Infectious Diseases*. These findings suggest that antiretroviral guidelines in developing countries should recommend a triple combination regimen for all HIV positive pregnant women regardless of CD4 cell count, as is the case in the U.S.

By Liz Highleyman

It is well known that use of *zidovudine (AZT; Retrovir)* and/or single-dose *nevirapine (Viramune)* during pregnancy and breast-feeding lowers the likelihood of mother-to-child HIV transmission. However, use of single or dual agents can promote drug resistance that potentially limits future treatment options.

Antiretroviral therapy (ART) guidelines in the U.S. and Europe recommend that all HIV positive pregnant women—regardless of CD4 T-cell count—should receive a complete 3-drug combination regimen, but this has typically not been standard practice for women with well-preserved immune function in resource-limited regions. Furthermore, public health experts advise that HIV positive mothers in poor countries should breast-feed their babies for at least the first 6 months to ensure adequate nutrition—contrary to recommendations in wealthy countries.

In the present study, Timothy Farley from the World Health Organization (WHO) and fellow investigators with the Kesho Bora Study Group assessed the safety and efficacy of a triple antiretroviral regimen compared with zidovudine plus single-dose nevirapine for prophylaxis against vertical HIV-1 transmission.

The analysis included nearly 900 HIV positive pregnant women enrolled from June 2005 through August 2008 at 5 sites in Burkina Faso, Kenya, and South Africa. Participants had WHO stage 1, 2, or 3 HIV-1 infection with CD4 counts of 200 to 500 cells/mm³. This made them ineligible for ART for their own health according to WHO guidelines in effect at the time, though the global treatment threshold has since been raised to 350 cells/mm³.

A total of 824 women were randomly assigned to receive either a triple antiretroviral combination or 2-drug prophylaxis starting at 28-36 weeks of gestation. The triple combination consisted of 300 mg zidovudine plus 150 mg *lamivudine (Epivir)* plus 400/100 mg *lopinavir/ritonavir (Kaletra)* twice-daily until cessation of breast-feeding, up to a maximum of 6.5 months post-partum.

The dual regimen consisted of 300 mg twice-daily zidovudine until delivery, with a 600 mg zidovudine dose plus a single 200 mg nevirapine dose at the onset of labor. In December 2006 the study protocol was amended to include 300 mg zidovudine plus 150 mg lamivudine, both twice-daily, for 1 week post-partum. In addition, all infants in both groups received a 0.6 mL dose of nevirapine at birth and, starting in December 2006, also 4 mg/kg zidovudine twice-daily for 1 week after birth.

**Results**

- Between June 2005 and August 2008, the 824 randomized women gave birth to 805 singleton or first live-born infants.
- The cumulative rate of HIV transmission at 6 weeks was 3.3% in the triple antiretroviral group compared with 5.0% in the zidovudine/single-dose nevirapine group—not a significant difference.
- By 12 months, however, the corresponding transmission rates were 5.4% in the triple combination group versus 9.5% in the dual prophylaxis group—a 43% relative risk reduction that did reach statistical significance (P = 0.029).
- The combined cumulative rate of HIV transmission or infant death at 12 months was 10.2% in the triple antiretroviral group compared with 16.0% in the dual regimen group, again statistically significant (P = 0.017).
- Considering only those infants whose mothers said they intended to breast-feed, the cumulative transmission rates at 12 months were 5.6% and 10.7%, respectively, representing a significant 48% reduction (P = 0.02).
Rate of late post-natal infection more than 6 weeks after birth were 2.2% in the triple antiretroviral group versus 4.7% in the dual prophylaxis group, a 53% risk reduction.

Women taking the triple combination regimen had higher median CD4 cell counts at the time of delivery and at 6 and 12 months post-partum, and a higher proportion had undetectable HIV viral load compared with the dual regimen group.

The incidence of laboratory and clinical serious adverse events among both mothers and infants was similar in the 2 groups.

Based on these findings, the study authors concluded, "Triple antiretroviral prophylaxis during pregnancy and breast-feeding is safe and reduces the risk of HIV transmission to infants."

"Revised WHO guidelines now recommend antiretroviral prophylaxis (either to the mother or to the baby) during breast-feeding if the mother is not already receiving antiretroviral treatment for her own health," they added.

The researchers noted that data on AIDS-free survival of mothers at 18 months will be reported later in another publication. The study leaves open the question of if and when women should stop combination antiretroviral therapy after giving birth if their CD4 count remains above the treatment initiation threshold.

Reference

NSAID receptor responsible for olive oil's 'cough' and more
Combination of sensory and molecular approaches identify receptor sensitive to anti-inflammatory compounds
PHILADELPHIA (January 18, 2011) – Scientists from the Monell Center and collaborators report that a receptor known as TRPA1 is activated by two structurally unrelated anti-inflammatory compounds. The first, oleocanthal, is a natural polyphenolic anti-inflammatory agent uniquely found in extra virgin olive oil; while the second, ibuprofen, is an over-the-counter non-steroidal anti-inflammatory drug (NSAID).

The researchers also demonstrate that the TRPA1 receptor is spatially localized to the back of the throat, which is exactly where the distinctive irritating sting from olive oil is felt. This unique sensation and the accompanying 'cough' are regarded among connoisseurs as indicators of high quality olive oil.

"We believe that the TRPA1 receptor elicits cough to protect the lungs from chemical insult, for example from toxins in the air," said Paul A.S. Breslin, Ph.D., one of the corresponding authors and a sensory biologist at Monell.

In 2005, Monell researchers and collaborators announced the discovery that oleocanthal is a non-steroidal, anti-inflammatory agent that inhibits activity of cyclooxygenase (COX) enzymes, a pharmacological action shared by ibuprofen.

The finding was based on the sensory observation that olive oil irritates the back of the throat in a highly characteristic manner identical to that experienced with liquid ibuprofen.

At that time, the researchers also demonstrated that oleocanthal caused the irritating throat sting associated with extra virgin olive oils.

The current study, published in the Journal of Neuroscience, extends those findings by identifying TRPA1 as the receptor that is activated by both oleocanthal and ibuprofen.

Further, the findings establish that oleocanthal causes the distinctive sting of olive oil through its activation of TRPA1. Similarly, activation of the same receptor produces ibuprofen's irritating sensation.

The findings may provide novel insights into anti-inflammatory pharmacology. "This receptor may be used to identify other anti-inflammatory compounds that, like ibuprofen and oleocanthal, help prevent major lethal disease," said Breslin.

"Additionally, since we know how to inhibit this receptor, it may be possible to develop liquid anti-inflammatory medicines that are less aversive. This would especially benefit children, who are unable to swallow pills."

The study's combination of sensory, chemical, and molecular approaches may lend insight into other aspects of inflammation and disease.

"Oleocanthal and ibuprofen are chemically unrelated, yet both are potent anti-inflammatory compounds that activate the TRPA1 receptor and cause sensory irritation," said Monell behavioral biologist Gary K. Beauchamp, Ph.D., also a corresponding author. "This points to a possible mechanistic
connection between sensory perception, receptor activation, and pharmacology. An understanding of this connection could someday lead to identification of new anti-inflammatory pathways."

Future work also will explore several paradoxical associations that relate the sensory and health-promoting aspects of oleocanthal and ibuprofen. Lead author Catherine Peyrot des Gachons, Ph.D., a food scientist at Monell, points out that the two anti-inflammatories promote health while also causing irritation and pain. She comments, "These two facts seem antagonistic and excitingly mysterious from a scientific perspective."

Beauchamp raises a related question, noting that humans have come to appreciate the 'pain' from oleocanthal in olive oil, as if there is an inner knowledge that it is advantageous. "How this happens remains a fascinating puzzle," he says.

**A new method to correct mortality rate biases in HIV treatment programs**

HIV treatment programs in sub-Saharan Africa should routinely report mortality rates among patients who remain in the programs and those patients lost to follow-up, according to a study by Matthias Egger and colleagues from the International Epidemiologic Databases to Evaluate AIDS in East Africa, Western Africa, and Southern Africa that is published in this week’s *PLoS Medicine*. As a substantial proportion of patients in HIV treatment programs are lost to follow-up, mortality estimates for patients in these programs can be severely underestimated, so this bias needs to be taken into account when comparing the effectiveness of different programs.

The authors arrived at these conclusions by developing a nomogram (calculator) that corrects mortality estimates for loss to follow-up, based on the fact that mortality of all patients starting antiretroviral therapy in an HIV treatment program is a weighted average of mortality among patients lost to follow-up and patients remaining in care.

In an accompanying Perspective, Gregory Bisson from the University of Pennsylvania School of Medicine (not involved in the research) comments that "currently we know little about the biology and behaviors that underlie loss to follow-up, but with 5.2 million people on [antiretroviral therapy], and more starting soon as a result of the 2010 WHO guidelines recommending HIV treatment earlier during disease progression, a greater understanding of loss to follow-up in its various forms is needed in order to keep the HIV treatment effort on track." He adds, "by addressing the effects of loss to follow-up on programmatic mortality estimates, and by providing monitoring efforts with a useful new tool, Egger and colleagues have helped address this need."

**Sex, race, and geography influence health outcomes following primary HIV infection**

Women, nonwhites, and people in the southern United States who were newly infected with HIV and followed for an average of four years experienced greater HIV/AIDS-related morbidity compared to men and people of other races living in other regions of the country. The findings, published in the February 15 issue of *The Journal of Infectious Diseases*, underscore the urgent need to improve the health of these populations in order to reduce HIV-related morbidity and mortality in the U.S. (Please see below for a link to the embargoed study online.)

The researchers did not expect women to show the worst health outcomes because their viral loads were lower and CD4+ T cell counts were higher than men’s following diagnosis, reported study author Amie L. Meditz, MD, of the University of Colorado- Denver. (The study was part of the Acute Infection and Early Disease Research Program, a multicenter study network funded by the National Institute of Allergy and Infectious Diseases.) However, during the course of the study (1997-2007), the frequency of HIV-related illnesses in women was more than double that of men, with nonwhite women having the most negative outcomes. After eight years of infection, HIV-related events affected 64 percent of nonwhite women, and AIDS-defining events occurred in 22 percent of nonwhite women. In comparison, HIV-related and AIDS-defining events occurred in 21 percent and 6 percent of individuals in other combined race and sex groups, respectively.

The data representing subjects from the southern U.S. show that race and region play a major role in health outcomes of both women and men infected with HIV. Eight years following their diagnosis, 78 percent of nonwhites and 37 percent of whites in the southern U.S. had experienced one or more HIV/AIDS-related event, compared to 17 percent of nonwhites and 24 percent of whites in other geographic locations.

According to the investigators, race-sex differences in response to antiretroviral therapy were nonexistent. The researchers observed that nonwhite women and men and individuals from the South
were not as likely as white men and individuals from other regions of the U.S. to initiate antiretroviral therapy. Nevertheless, use of antiretroviral therapy only explained part of the differences in outcomes. The authors hypothesized that the disparities could be attributed to the influence of socioeconomic factors, including “access to health care, health behaviors, lifestyle, and environmental exposures.” Delayed therapy may be one factor affecting increased morbidity in HIV-infected individuals living in the South; however, socioeconomic factors probably also play a role.

In an accompanying editorial, Carlos del Rio, MD, and Wendy S. Armstrong, MD, of Emory University’s Center for AIDS Research in Atlanta, commented on the challenges presented in the study. The likelihood of HIV-infected individuals seeking care depends on factors not related purely to biology, and it is critical to consider socioeconomic factors when developing care strategies for these individuals. They noted that "socioeconomic factors play a much more important role in determining HIV disease outcomes, both at an individual as well as at a population level, and although theoretically modifiable, they represent complex challenges that are beyond the traditional influence of public health."

Dr. Meditz concluded that "understanding the causes of poor health outcomes among HIV-infected women, nonwhites and people from the South is a critical first step. In addition, development of strategies or interventions to improve health outcomes in these populations is essential."

**Fast Facts:**
1. The researchers evaluated data from more than 2,000 primarily North American patients who were identified within a year of acquiring HIV infection and then were followed for an average of four years.
2. The majority of men (77 percent) in the study were white, while the majority of women (55 percent) were nonwhite. Almost half (45 percent) of nonwhite women were from the southern U.S., and 79 percent of women from the South were nonwhite.
3. Antiretroviral therapy was less likely to be started at any time point by nonwhite women and men compared to white men and by individuals from the southern U.S. compared to others.
4. Women were 2.17-fold more likely to experience more than one HIV/AIDS-related event than men. Further, nonwhite women were most likely to experience an HIV/AIDS-related event compared to all others.
5. In the study, 78 percent of nonwhites and 37 percent of whites from the southern U.S. experienced more than one HIV/AIDS-related event eight years after diagnosis, compared to 24 percent of whites and 17 percent of nonwhites from other regions.

**New research examines how HIV infections occur on the molecular level**
The UK’s National Physical Laboratory (NPL) with the University of Edinburgh and IBM’s TJ Watson Research Center have published new research about the structure of an HIV-1 protein that could help to develop new drugs to stop the virus infecting healthy cells.

The research provides a new insight into how the changes in structure of a small part of an HIV protein (a membrane proximal peptide) may alter the infection of the virus into healthy cells. The team was able to observe key changes in this part of the protein implicated in the early stages of the infection by using a combination of powerful experimental and computational tools. This is the first attempt to demonstrate that the inducible binding of the peptide with membrane-like surfaces can serve as a responsive molecular anchor underpinning HIV fusion to target cells.

This information is important as it gives us a better understanding of how HIV infections take hold at the molecular level. Drug designers could use this information to develop treatments that stop HIV from entering a healthy cell and infecting it.

This research is a part of the NPL-led international research project ‘Multiscale measurements in biophysical systems’, which is jointly funded by NPL and the Scottish Universities Physics Alliance.

The team’s journal article detailing this research was selected as the featured article in the January 2011 issue of the journal *Physical Chemistry Chemical Physics* – the Royal Society of Chemistry’s premier forum for physical chemistry research.

**Increase in stroke among HIV-positive patients in US**
Michael Carter
Published: 19 January 2011

The proportion of US patients hospitalised because of stroke who are HIV-positive has increased significantly in recent years, investigators report in *Neurology*. This was at a time when stroke hospitalisations in the general US population were falling.

“There was a significant rise of approximately 67% in the proportion of patients hospitalized for stroke who had prevalent HIV infection,” write the investigators, who attribute this increase to “evolving
circumstances unique to HIV-infected patients” such as the inflammatory effects of long-term infection with the virus.

Investigators undertook the study because there is little information on stroke prevalence for patients with HIV and its risk factors. They believed that such a study was especially timely as many patients with HIV are now surviving into middle and older age, and because research suggests that both HIV itself and possibly its treatment can increase the risk of cardiovascular diseases.

Individuals hospitalised for stroke between 1997 and 2006 were included in the study. Data were collected from across the US from hospitals that contributed information to the National Inpatient Sample.

Both HIV-positive and HIV-negative patients were categorised according to the type of stroke causing hospitalisation: ischemic, caused by a blocked artery, or haemorrhagic, caused by bleeding into the brain. In 1997, 0.09% of all patients hospitalised because of stroke were HIV-positive and this increased significantly to 0.15% in 2006 (p < 0.001).

At the same time, there was a 7% fall in stroke hospitalisations among the general US population (100,000 per year to 97,000 per year).

Actual numbers of stroke hospitalisations involving patients with HIV increased 43% from 888 in 1997 to 1425 in 2006.

Furthermore, after 2001 the rate of hospitalisations for HIV-positive patients increased by approximately 43% from 90 per 100,000 in 2001 to 129 hospitalisations per 100,000 in 2006. This increase was significant (p = 0.02).

The proportion of patients hospitalised because of ischaemic stroke more than doubled during the study (0.08% in 1997; 0.18% in 2006, trend p < 0.001). However, the proportion of strokes caused by haemorrhage remained stable. The investigators describe these findings as “noteworthy.”

Median age among the HIV-positive patients experienced stroke was 43 years in 1997 and 48 years in 2006.

Factors independently associated with increased risk of stroke for HIV-positive individuals included well-established demographic risk factors including male sex, older age and black race (all p < 0.0001).

Other health problems also increased the risk of stroke, such as a history of heart attack (p = 0.03), peripheral vascular disease (p < 0.0001), dementia (p < 0.0001), liver disease (p < 0.0001), diabetes (p < 0.0001), kidney disease (p < 0.0001) and cancer (p < 0.0001).

“Although the absolute numbers of stroke hospitalizations with HIV infection are relatively small…this steep rise over a short period of time may be of public health concern,” write the investigators. Although their study was unable to show why there had been this increase the investigators speculate, “HIV infection or its treatment is directly related to the stroke pathophysiology in this population.”

"The average age for a stroke among people with HIV was in the 50s, which is much lower than that of those without HIV. This finding suggests that HIV or HIV treatments may be directly related to stroke occurrence," said Dr Bruce Ovbiagele of University of California at San Diego, who carried out the study with Dr Avindra Nath of Johns Hopkins University, Baltimore.

"Indeed, one potential explanation is the increasingly widespread use of combination antiretroviral medications in HIV-infected people. While these therapies have greatly increased life expectancy, they may boost the presence of risk factors associated with stroke. Another possibility is that longer exposure to HIV as a result of greater survival, even at low viral load levels, may allow for the virus to increase stroke risk."

Reference


On Tuesday’s discussion at the 128th Executive Board on the Draft WHO HIV/AIDS strategy 2011–2015, the United States made a strong intervention (delivered by Dr. Nils Daulaire, Director, Office of Global Health Affairs, Department of Health and Human Services) in support of the Medicines Patent Pool drawing attention to the fact that the draft HIV/AIDS strategy while making reference to a more competitive market for ARVs, failed to recognized the importance of the Medicines Patent Pool.

Here below are the remarks of the US on this point:

Finally, but importantly, the Strategy makes several references to the need to foster an open competitive market for ARVs to contain ARV costs, but does not recognize the importance of voluntary
licenses and the Medicines Patent Pool as key opportunities for ensuring that that happens. The Strategy
does encourage the use of differential pricing for patent protected medicines to ensure affordable access,
but recent studies have demonstrated that differential pricing does not always have the impact on the
pricing of medicines that robust generic competition does. The Medicines Patent Pool aims to enhance
competition to bring down the prices in developing countries, which the strategy advocates. The Pool can
also encourage needed new innovation, especially to help treat children and create fixed-dose
combinations necessary to scaling up and improving HIV treatment in resource poor settings. The initial
license from the U.S. National Institutes of Health to the Medicines Patent Pool announced in September
was an important first step, but to succeed it is critical to have more companies joining the Pool to scale
up HIV treatment.

High-Dose Vitamin D3 During Intensive-Phase Antimicrobial Treatment of
Pulmonary Tuberculosis: A Double-Blind Randomized Controlled Trial
The Lancet doi:10.1016/S1040-1673(10)61889-2, (01.06.2011) Dr. Adrian R. Martineau, MRCP, and
others
“Vitamin D was used to treat tuberculosis in the pre-antibiotic era, and its metabolites induce
antimycobacterial immunity in vitro. Clinical trials investigating the effect of adjunctive vitamin D on
sputum culture conversion are absent,” explained investigators.

In their multi-center randomized controlled trial of adjunctive vitamin D in adults with sputum
smear-positive TB in London, the researchers designated 146 patients to receive either 2.5 mg vitamin D3
or placebo at baseline and at 14, 28 and 42 days after initiating standard TB treatment. The primary
endpoint was time from start of antimicrobial treatment to sputum culture conversion. Participants were
genotyped for TaqI and FokI polymorphisms of the vitamin D receptor, and interaction analyses were
performed to assess the influence of the vitamin D receptor genotype on the vitamin D3 response.

The primary efficacy analysis included 126 patients (62 in intervention group, 64 in placebo group).
Median time to sputum culture conversion was 36.0 days in the intervention group and 43.5 days in the
placebo group (adjusted hazard ratio 1.39, 95 percent confidence interval 0.90-2.16; p=0.14). TaqI
genotype modified the effect of vitamin D supplementation on sputum culture conversion time (p
interaction=0.03), with enhanced response seen only in patients with the tt genotype (8.09, 95 percent CI
1.36-48.01; p=0.02). FokI genotype was not found to modify the effect of vitamin D supplementation (p
interaction=0.85). “Mean serum 25-hydroxyvitamin D concentration at 56 days was 101.4 nmol/L in the
intervention group and 22.8 nmol/L in the placebo group (95 percent CI for difference 68.6-
88.2;p<0.0001),” according to the results.

“Administration of four doses of 2.5 mg vitamin D3 increased serum 25-hydroxyvitamin D
concentrations in patients receiving intensive-phase treatment for pulmonary tuberculosis. Vitamin D did
not significantly affect time to sputum culture conversion in the whole study population, but it did
significantly hasten sputum culture conversion in participants with the tt genotype of the TaqI vitamin D
receptor polymorphism,” the investigators concluded.

Hospital Visitation Rights for Same-Sex Partners Now Required by Federal Rules
Under new federal regulations that took effect Tuesday, hospitals that receive Medicaid and Medicare
funding are barred from having visitation policies that discriminate based on sexual orientation. In the
past, such policies allowed only those related by blood or marriage to visit an incapacitated person. Gay
rights advocates also said many hospitals refused to allow members of same-sex couples to authorize their
partner to make crucial medical decisions on their behalf. Any hospital that violates the new regulations
will risk losing its federal funding. “This new policy will have a positive impact on same-sex couples and
our families throughout the nation,” said Rea Carey, executive director of the National Gay and Lesbian
Task Force.

Nature News Examines Haiti Cholera Vaccine Debate, Developments
Nature News reports on developments related to the plan for a cholera vaccination campaign in Haiti
and experts’ varying opinions about how to proceed. “Most experts in the international community
recommend a limited pilot project that would determine whether to scale up and how to use cholera
vaccines in future outbreaks elsewhere. The Haitian government, caught in a febrile political environment
and fearful that those denied vaccination might feel resentful, is demanding immediate, broad coverage," Nature News writes.

An expert committee, convened by the WHO, met in December and "decided that vaccination should be tried," Nature News notes. "On 13 January, the expert committee, including representatives from the WHO, the U.S. Centers for Disease Control and Prevention, the U.S. National Institutes of Health (NIH), UNICEF, the U.S. National Vaccine Program Office and others, held a teleconference to fine-tune a vaccination plan that could form the basis of a more detailed WHO-coordinated campaign strategy. The committee is recommending a pilot project using the currently available 250,000–300,000 doses of Dukoral, and the creation of a stockpile of the vaccine for the future." According to the news service, "Dukoral has not been used on such a scale before, although studies of thousands of people have shown it to be about 80% effective. The committee has not worked out where the campaign would be focused."

The article notes some of the challenges facing the vaccination campaign. "Although vaccine drives in Africa and elsewhere have faced resistance, Haitian people are eager to be vaccinated, says Francois Lacapere, a vaccine expert for Pan American Health Organization (PAHO)/WHO in Haiti. Yet many Haitians are also sceptical of aid agencies' motives. ... Even if the programme can win enough trust, using the world's entire stockpile of doses would still leave most Haitians without vaccine — a controversial prospect for the beleaguered government," the news service writes.

Jean Ronald Cadet, the vaccination program manager at the Haitian health ministry, said the country is "90 percent" ready to go ahead with a vaccination campaign, but said the WHO's pilot plan is too small. "He insists that Haiti would only consider starting to vaccinate with more than 1 million doses, with a goal of eventually reaching 6 million people. 'It would depend on the pressure that the international community can put on manufacturers.'' In response to a question about who would pay for the vaccine, Cadet responded, "The international community. They brought us cholera, they have to take responsibility for taking care of it."

The article also looks at the viability of scaling up vaccine production and includes opinions from health experts about the size of the campaign. Kate Alberti, a Medecins Sans Frontieres epidemiologist; Jon Andrus, deputy director of PAHO; Jean-Claude Mubalama, UNICEF's chief of health in Haiti; Renaud Piarroux, an epidemiologist at the University of the Mediterranean; and Matthew Waldor, an infectious-disease expert at Harvard Medical School are quoted in the article (Cyranoski, 1/18).

Study finds celiac patients can eat hydrolyzed wheat flour
Baked goods made from hydrolyzed wheat flour are not toxic to celiac disease patients, according to a new study in Clinical Gastroenterology and Hepatology, the official journal of the American Gastroenterological Association (AGA) Institute. Celiac disease occurs in the digestive system when people cannot tolerate a protein called gluten, which is found primarily in wheat.

"This is the first time that a wheat flour-derived product is shown to not be toxic after being given to celiac patients for 60 days," said Luigi Greco, MD, PhD, of the University of Napes, Italy, and lead author of the study. "Our findings support further research that explores therapies that could reduce the toxicity of gluten for celiac patients beyond the standard gluten-free diet."

Gluten is also primarily found in barley and rye, but may be in everyday products such as soy sauce and salad dressing, as well as some medications and vitamins. Celiac disease was, until recently, thought to be a rare disease. However, recent research has shown that as many as three million people in the U.S. may have celiac disease.

In this study, doctors evaluated the safety of daily administration of baked goods made from a hydrolyzed form of wheat flour to patients with celiac disease. The doctors fermented wheat flour with sourdough lactobacilli and fungal proteases; this process decreases the concentration of gluten.

A total of 16 patients with celiac disease, ranging in age from 12 to 23 years were evaluated. They were in good health on a gluten-free diet for at least five years. Two of the six patients who ate natural flour baked goods discontinued the study because of symptoms such as malaise, abdominal pain and diarrhea. The two patients who ate extensively hydrolyzed flour baked goods had no clinical complaints, but developed subtotal atrophy (complete absence of villi, the fingerlike protrusions necessary for absorption). The five patients that ate the fully hydrolyzed baked goods had no clinical complaints.

"Prolonged trials have to be planned to underscore the safety of baked goods made by applying the rediscovered and adapted biotechnology of hydrolysis. In the future, cereals made through such biotechnology could also improve the nutritional and sensory properties of baked goods containing hydrolyzed gluten compared to products made of naturally gluten-free ingredients," added Dr. Greco.
Malaria Parasite Caught Red-Handed Invading Blood Cells

ScienceDaily (Jan. 19, 2011) — Australian scientists using new image and cell technologies have for the first time caught malaria parasites in the act of invading red blood cells. The researchers, from the Walter and Eliza Hall Institute in Melbourne, Australia, and the University of Technology, Sydney (UTS), achieved this long-held aim using a combination of electron, light and super resolution microscopy, a technology platform new to Australia.

The detailed look at what occurs as the parasite burrows through the walls of red blood cells provides new insights into the molecular and cellular events that drive cell invasion and may pave the way for developing new treatments for malaria. Institute researchers Dr Jake Baum, Mr David Riglar, Dr Dave Richard and colleagues from the institute’s Infection and Immunity division led the research with colleagues from the i3 institute at UTS.

Dr Baum said the real breakthrough for the research team had been the ability to capture high-resolution images of the parasite at each and every stage of invasion, and to do so reliably and repeatedly. Their findings are published in today’s issue of the journal Cell Host & Microbe.

"It is the first time we’ve been able to actually visualise this process in all its molecular glory, combining new advances developed at the institute for isolating viable parasites with innovative imaging technologies," Dr Baum said.

"Super resolution microscopy has opened up a new realm of understanding into how malaria parasites actually invade the human red blood cell. Whilst we have observed this miniature parasite drive its way into the cell before, the beauty of the new imaging technology is that it provides a quantum leap in the amount of detail we can see, revealing key molecular and cellular events required for each stage of the invasion process."

The imaging technology, called OMX 3D SIM super resolution microscopy, is a powerful new 3D tool that captures cellular processes unfolding at nanometer scales. The team worked closely with Associate Professor Cynthia Whitchurch and Dr Lynne Turnbull from the i3 institute at UTS to capture these images.

"This is just the beginning of an exciting new era of discoveries enabled by this technology that will lead to a better understanding of how microbes such as malaria, bacteria and viruses cause infectious disease," Associate Professor Whitchurch said.

Dr Baum said the methodology would be integral to the development of new malaria drugs and vaccines. "If, for example, you wanted to test a particular drug or vaccine, or investigate how a particular human antibody works to protect you from malaria, this imaging approach now gives us a window to see the actual effects that each reagent or antibody has on the precise steps of invasion," he said.

Malaria is caused by the Plasmodium parasite, which is transmitted by the bite of infected mosquitoes. Each year more than 400 million people contract malaria, and as many as a million, mostly children, die.

"Historically it has been very difficult to both isolate live and viable parasites for infection of red blood cells and to employ imaging technologies sensitive enough to capture snapshots of the invasion process with these parasites, which are only one micron (one millionth of a metre) in diameter," Dr Baum said.
He said one of the most interesting discoveries the imaging approach revealed was that once the parasite has attached to the red blood cell and formed a tight bond with the cell, a master switch for invasion is initiated and invasion will continue unabated without any further checkpoints.

"The parasite actually inserts its own window into the cell, which it then opens and uses to walk into the cell, which is quite extraordinary," Dr Baum said. "Visually tracking the invasion of Plasmodium falciparum into a red blood cell is something I've been aiming at ever since I began at the Walter and Eliza Hall Institute in 2003; it's really thrilling to have reached that goal. This technology enables us to look at individual proteins that we always knew were involved in invasion, but we never knew what they did or where they were, and that, we believe, is a real leap for malaria researchers worldwide."

Journal Reference:
David T. Riglar, Dave Richard, Danny W. Wilson, Michelle J. Boyle, Chaitali Dekiwadia, Lynne Turnbull, Fiona Angrisano, Danushka S. Marapana, Kelly L. Rogers, Cynthia B. Whitchurch, James G. Beeson, Alan F. Cowman, Stuart A. Ralph, Jake Baum. 
Super-Resolution Dissection of Coordinated Events during Malaria Parasite Invasion of the Human Erythrocyte. 
Cell Host & Microbe, Volume 9, Issue 1, 9k20, 20 January 2011 DOI: 10.1016/j.chom.2010.12.003

In Scientific First, Researchers Visualize Naturally Occurring mRNA

ScienceDaily (Jan. 19, 2011) — In a technique that could eventually shed light on how gene expression influences human disease, scientists at Albert Einstein College of Medicine of Yeshiva University have for the first time ever successfully visualized single molecules of naturally-occurring messenger RNA (mRNA) transcribed in living mammalian cells.

The scientific achievement is detailed in the January 16 online edition of Nature Methods.

Gene expression involves transcribing a gene’s DNA into molecules of mRNA. These molecules then migrate from a cell’s nucleus into the cytoplasm, where they serve as blueprints for protein construction.

Robert Singer, Ph.D., codirector of the Gruss Lipper Biophotonics Center and professor and cochair of anatomy and structural biology, was senior author of the paper. Working with his colleagues, he generated a transgenic mouse in which genes coding for the structural protein beta actin would, when expressed, yield fluorescently labeled mRNA. Beta actin mRNA is a highly expressed molecule found in all mammalian tissues.

The technique used by the Einstein researchers should be applicable for monitoring the expression of any gene of interest. Prior to this study, Einstein researchers had monitored mRNA molecules transcribed by artificial genes.

"Our report is the first demonstration that our technique can be used to visualize the expression of an essential gene in mammalian cells," said Timothée Lionnet, Ph.D., a research fellow in Dr. Singer’s lab and lead author of the Nature Methods paper. "We can study beta actin RNA molecules over their life..."
cycle in a variety of cell types and discover where they are distributed within the cell. This has important
consequences for human disease like cancer, since the way molecules of mRNA are localized within tumor
cells correlates with the ability of these cells to spread, or metastasize."

**Journal Reference:**
Timothée Lionnet, Kevin Czapinski, Xavier Darzaccq, Yaron Shav-Tal, Amber I Wells, Jeffrey A Chao, Hye Yoon Park, Valeria de Turris, Melissa Lopez-Jones, Robert H Singer. *A transgenic mouse for in vivo detection of endogenous labeled mRNA.*
*Nature Methods*, 2011; DOI: 10.1038/nmeth1551

Nearly half of HIV-positive women in TN unaware of contraceptives: Study
Revathi Ramanan, TNN, Jan 20, 2011, 04.45am IST
CHENNAI: In a survey conducted among 986 HIV-positive women in 13 high-prevalence districts across Tamil Nadu, it was found that a shocking 48% of them had no knowledge about contraceptives.

The survey, which analysed the reproductive, child and sexual health needs of women living with HIV/AIDS in the state, also showed that over 60% of them had never heard of cervical cancer and pap smear tests even though HIV-positive women are more susceptible to cervical and breast cancer. As many as 70% of the women surveyed were daily wage labourers and belonged to the lower economic class with a monthly income of less than Rs 5,000 a month.

More than half the women were not aware of the various sexually transmitted infections (STI) and only 3% of the women could guess that an STI was a problem related to the genitals. The survey also revealed that most HIV-positive women (60.4%) did not share information on STIs with their adolescent children and had inhibitions about discussing about sex and sexuality with their children.

The results of the survey were released during a four-day leadership training programme for HIV positive women from 10 states organised by United Nations Development Programme (UNDP), Tamil Nadu State AIDS Control Society (TANSACS) and National AIDS Control Organisation (NACO) along with the Positive Women Network (PWN).

The programme hopes to address the various issues faced by HIV positive women across the country such as those related to property, violence, livelihood and sexual health. As many as 27 women from various states participated in the event and presented case studies about the various problems faced by the HIV-positive women in their respective states. The authors of 15 best case studies will be given a one-time stipend of Rs 20,000 to implement their ideas within a period of three months.

"In Tamil Nadu, one of the major issues is of women not having property rights. It is important for a HIV-positive woman to have some property to support her. If my case study is chosen, I will work towards raising awareness about this issue," said D Padmavathy, president of Tamil Nadu PWN. Varsha Gaekwad, president of Maharashtra PWN, said that issues of reproductive health plagued women in the states of Maharashtra and Gujarat and she hoped to address these issues and conduct awareness camps for women in the state about cervical cancer, breast cancer and other sexually transmitted diseases.

Double whammy for HIV
RNA dynamic duo curbs infection in mice.
Cassandra Willyard
An RNA molecule engineered to attack HIV in two different ways is showing positive results, according to a study in *Science Translational Medicine*. The researchers say that the molecule, which both curbs viral replication inside infected cells and neutralizes free-floating virus, could help patients who have developed resistance to HIV drugs.

The molecule, known as a chimaera, is composed of two different types of RNA: a small interfering RNA (siRNA), designed to enter infected cells and block the expression of two genes that HIV needs to replicate, and an RNA sequence known as an aptamer, which binds tightly to gp120, a protein found on the surface of HIV and HIV-infected cells. The aptamer has a dual role: it ferries the siRNA into infected cells and it neutralizes free-floating virus in the blood.

John Rossi, a molecular biologist at the Beckman Research Institute of the City of Hope in Duarte, California, a lead author on the paper, describes the molecule as a smart bomb. "You're only targeting what has to be targeted," he says.

The chimaera is not new, but this is the first time it has been tested in animals. To test the chimaera, the team used mice engineered to be susceptible to HIV. When the researchers injected mice with either the chimaera or the aptamer alone, the amount of virus circulating in the animals' blood fell markedly. The chimaera, however, was more potent and suppressed the virus for a week longer than just the aptamer.
Rossi says that the molecule could be used as a stand-alone therapy, or in combination with other drugs that treat HIV. Because the antiviral effect of the chimaera lasts only about a week, patients would need to have regular injections.

**Not pulling its weight**

"This molecule, this design, is beautiful," says Ben Berkhout, a retrovirologist at the University of Amsterdam. But he is not entirely convinced that the siRNA has much of an impact. "They do see quite dramatic inhibition" of HIV, he says. But most of that inhibition seems to be due to the aptamer, not the siRNA. "I haven’t seen the double action of this combination," he says.

The researchers found the siRNA in white blood cells known as lymphocytes of mice treated with the chimaera, indicating that the molecule can get where it needs to be. And when they measured the expression of the two genes targeted by the siRNA — tat and rev — in those same cells, they found a 75–90% reduction in expression after treatment. They also saw that the siRNA was cleaving the tat and rev genes in the right spots, an indication that the molecule worked the way it was supposed to.

But Phillip Sharp, a molecular biologist at the Massachusetts Institute of Technology in Cambridge, says that although the study shows some siRNA activity in the lymphocytes of the mice, it "doesn’t show that most of the lymphocytes have siRNA activity. The question is how effectively is the siRNA internalized and utilized."

Because the chimaera doesn’t kill infected cells, it won’t cure HIV. The next step, says Rossi, is to use a chimaera to deliver siRNAs that can kill infected cells. "What you want to do is start purging the infected cell population," he says.

**References**


**Scientists reveal complete structure of HIV's outer shell**

The research from scientists at Scripps Research and UVa provides clues for new therapies by shedding light on how the outer coating of the virus forms

LA JOLLA, CA – A team of scientists at The Scripps Research Institute and the University of Virginia has determined the structure of the protein package that delivers the genetic material of the human immunodeficiency virus (HIV) to human cells.

The work is the culmination of studies carried out over the last decade looking at different portions of the cone-shaped container, or the capsid. The final piece of the puzzle, described in an article published in *Nature* on January 20, 2011, details the structure of the two ends of the cone.

"This paper is a real milestone for research from our group," says the study's senior author Mark Yeager, M.D., Ph.D., a Scripps Research professor and staff cardiologist and chair of the Molecular Physiology and Biological Physics Department at The University of Virginia School of Medicine.

A detailed description of the complete HIV capsid will provide a roadmap for developing drugs that can disrupt its formation and thus prevent infection by HIV.

**Assembling the Package**

HIV binds to receptors on human cells and then delivers the capsid inside them. Once inside a cell, the capsid comes apart, releasing its precious cargo—the virus's genetic material.

HIV then sabotages the cell machinery to make many copies of its genes and proteins. As new viruses are made, the genetic material is packaged into spherical immature capsids that HIV uses to escape from the infected cell. But before these newly released viruses can infect other cells, the immature capsid undergoes a dramatic rearrangement to form the mature, cone-shaped shell.

If formation of the mature capsid is disrupted, the virus is no longer infectious. Thus, new drugs targeting capsid formation could provide valuable additions to the arsenal of existing drugs against HIV.

**A "Floppy" Bridge**

To develop drugs that disrupt capsid formation, however, scientists first need to know precisely how it is formed.

One technology researchers use to obtain detailed structures of biological molecules is X-ray crystallography. This technique requires growing crystals of a molecule and then bombarding the crystals with X-rays to determine the positions of all the atoms.

But unlike the cone-shaped capsids of other viruses, such as the poliovirus, which have a rigid, symmetrical structure that obediently assembles into crystals, the HIV capsid is flexible and can adopt slightly different shapes.
Part of the reason for this flexibility is the protein that makes up the HIV capsid, the CA protein, consists of two ends held together by a "floppy" bridge.

In the capsid, each CA protein joins hands with other CA proteins, forming groups of five or six proteins. The main body of the capsid contains about 250 of the six-fold units or hexamers. Each end of the cone is then closed off by either five or seven smaller five-fold units or pentamers.

"It is impossible to grow crystals of the entire HIV capsid," says Yeager. As a result, his team used a "divide and conquer approach."

**Divide and Conquer**

Working with husband-and-wife team Owen Pornillos and Barbie Ganser-Pornillos, investigators in his lab, Yeager partitioned the HIV capsid into smaller components, then determined their respective structures.

Yeager's group started by focusing on the structure of the CA hexamer. A breakthrough came in 2007, when the group viewed the CA hexamers with a powerful electron microscope. Guided by information from that structure, in 2009 the team managed to trick the CA hexamers into forming crystals. The researchers were then able to determine the particles' structures at 2-Angstrom resolution (one Angstrom equals one ten-billionth of a meter).

Having cracked the atomic structure of the hexamer, the investigators turned their attention to the more elusive pentamers.

**Next Came the Pentamer**

In this latest study, Yeager, Pornillos, and Ganser-Pornillos used techniques similar to those they had applied to the hexamers to obtain the crystal structures of the CA pentamers.

The new structure reveals that five CA proteins link hands at one end, called the N-terminal domain (NTD), to form a circle. The opposite ends of the CA proteins, called C-terminal domain (CTD), form a floppy belt around this central core. Then, CTD links to CTD to connect adjacent pentamers.

The structure reveals flexibility and mobility both between the central core and belt within each pentamer and at the CTD-CTD interfaces of adjacent pentamers. The CTD subunits can rotate relative NTDs. "As a result, each ring can adopt slightly different angles relative to its adjacent rings," says Pornillos, first author of the paper.

The structure of the pentamers is remarkably similar to that of the hexamers, notes Pornillos, with one important difference. Because pentamers are smaller than hexamers, the amino acids, the building blocks of proteins, at the center of the pentamer ring are closer together than in the hexamer.

Many amino acids have positive or negative charges. When two amino acids with the same charge are close together they tend to push each other away. One amino acid in the CA protein, called arginine, with a positive charge, sits smack in the middle of both the hexamer and pentamer ring.

Because in the pentamer the arginines are packed much closer together, they repel one another, making the pentamer a less stable structure than the hexamer. This may explain why there are many more hexamers in the mature HIV capsid compared to pentamers.

The only place where pentamers are likely to form is at the capsids' ends, where the linked CA proteins have to bend dramatically to close off the capsid—a feat the pentamer is more apt to perform.

"Arginine is the critical switch between hexamer and pentamer formation," says Yeager. "We can finally explain why the CA protein would make one or the other."

**An Atomic Model of the HIV Capsid**

Having solved the atomic structures of both CA hexamers and pentamers, Yeager and colleagues for the first time were able to build a complete atomic model of the mature HIV capsid.

The researchers now plan to further refine the model using sophisticated computer programs to determine the stability of the structure in different regions and to identify possible "weak" points they can target using newly designed drugs.

They will also begin studying the structure of the immature capsid to determine how this version of the capsid transitions to the mature form—a step in the virus lifecycle that has remained mysterious. "We don't have the full story yet, but we have volume one," says Yeager.

January 19, 2011

**Manufacturer Recalls Alcohol Swab Products Packaged with Fuzeon, Other Meds**

Triad Group, a manufacturer of alcohol prep pads, alcohol swabs and alcohol swab sticks, announced that it is recalling all of these products because of concerns that they may be contaminated with a bacterium known as *Bacillus cereus*. The Triad Group alcohol prep pads are co-packaged and distributed with some
medications used by people living with HIV, including Genentech’s Fuzeon (enfuvirtide) and Pegasys (pegylated interferon, used to treat chronic hepatitis C virus infection).

This bacterium, typically found in the soil, can cause diarrhea and vomiting when it infects humans and can be life threatening in people with compromised immune systems. Triad Group says it has received one report of a non-life-threatening infection from this bacterium associated with its alcohol swab products.

In a statement of its own, Genentech noted that its medicines are not contaminated and may continue to be used in accordance with the package insert. However, the company warns that patients and health care providers should not use the alcohol prep pads packaged with these medicines and should instead use an alternate alcohol prep pad that is not involved with the Triad Group recall, or alternatively use a sterile gauze pad in conjunction with isopropyl alcohol for disinfecting the injection site prior to administration.

Genentech is in discussion with the U.S. Food and Drug Administration and is currently assessing alternatives to address the situation.

People who have used any Triad Group products and developed an infection from Bacillus cereus are also encouraged to contact the U.S. Food and Drug Administration (FDA) to report the incident; that website is http://www.fda.gov/MedWatch/report.htm, and the fax number is 1-800-FDA-0178.

Inadequate Fight Against Drugs Hampers Russia’s Ability to Curb HIV


Maxim, a graying 33-year-old Russian heroin addict with telltale scarred arms, circles a Moscow pharmacy known to sell prescription drugs illicitly. Another man with quarter-sized holes gouged into his body from injection-related infections declined to give his name, fearing arrest if he sought treatment for his addiction.

These men personify a Russian HIV epidemic that has raged since the Soviet collapse 20 years ago. According to UNAIDS, Russia reported 60,000 new cases of HIV in 2009, an 8 percent increase from 2008. More than 60 percent of those infections are attributed to drug injection, while many others are related to sex with intravenous drug users (IDUs).

Officials estimate that more than 1 million people in Russia are IDUs, often sharing tainted needles and infecting one another. In 2011, the government plans to double spending on HIV drugs to $600 million and expand prevention programs focusing on youths, said Galina G. Chistyakova, a Health Ministry official who helps oversee the country’s HIV/AIDS policies.

Although the government has increased efforts to fight HIV/AIDS, sex education and preventive programs such as needle exchange and drug substitution therapy have been denounced by top medical and political officials, as well as by the Russian Orthodox Church. According to the Federal Drug Control Service, 90 percent of Russian addicts use Afghan heroin, which officials blame on a US inability to eradicate production of heroin in Afghanistan.

Lev Zohrabyan, Europe and Central Asia adviser for UNAIDS, identified IDUs and sex workers as groups to focus funds on to effect change but noted that Russia’s budget for the next two years makes no provisions for prevention work among them.

“I've been researching the problem of HIV infection for 25 years,” said Dr. Vadim V. Pokrovsky, head of Russia’s Federal AIDS Center, “and I must say the situation has become significantly worse.”

Long-distance migration may help reduce infectious disease risks for many animal species

Athens, Ga. – It’s a common assumption that animal migration, like human travel across the globe, can transport pathogens long distances, in some cases increasing disease risks to humans. West Nile Virus, for example, spread rapidly along the East coast of the U.S., most likely due to the movements of migratory birds. But in a paper just published in the journal Science, researchers in the University of Georgia Odum School of Ecology report that in some cases, animal migrations could actually help reduce the spread and prevalence of disease and may even promote the evolution of less-virulent disease strains.

Every year, billions of animals migrate, some taking months to travel thousands of miles across the globe. Along the way, they can encounter a broad range of pathogens while using different habitats and resources. Stopover points, where animals rest and refuel, are often shared by multiple species in large aggregations, allowing diseases to spread among them.
But, according to Odum School associate professor Sonia Altizer and her co-authors, Odum School postdoctoral associates Rebecca Bartel and Barbara Han, migration can also help limit the spread of some pathogens.

Some kinds of parasites have transmission stages that can build up in the environment where host animals live, and migration allows the hosts to periodically escape these parasite-laden habitats. While hosts are gone, parasite numbers become greatly reduced so that the migrating animals find a largely disease-free habitat when they return. Long migratory journeys can also weed infected animals from the population: imagine running a marathon with the flu. This not only prevents those individuals from spreading disease to others, it also helps to eliminate some of the most virulent strains of pathogens.

"By placing disease in an ecological context," said Odum School dean John Gittleman, "you not only see counterintuitive patterns but also understand advantages to disease transmission. This is a classic example of disease ecology at its best."

Altizer's long-term research on monarch butterflies and a protozoan parasite that infects them provides an excellent demonstration of migration's effects on the spread of infectious disease. Monarchs in eastern North America migrate long distances, from as far north as Canada, to central Mexico, where they spend the winter. Monarchs in other parts of the world migrate shorter distances. In locations with mild year-round climates, such as southern Florida and Hawaii, monarchs do not migrate at all. Work by Altizer and others in her lab showed that parasite prevalence is lowest in the eastern North American population, which migrates the farthest distance, and highest in non-migratory populations. This could be because infected monarchs do not migrate successfully, as suggested by tethered-flight experiments with captive butterflies, or because parasites build up in habitats where monarchs breed year-round. Other work showed that parasites isolated from monarchs that flew the longest were less virulent than those found in monarchs that flew shorter distances or didn't migrate at all, suggesting that monarchs with highly virulent parasites didn't survive the longest migrations.

"Taken together, these findings tell us that migration is important for keeping monarch populations healthy—a result that could apply to many other migratory animal species," said Altizer.

But for monarchs, and many other species, migration is now considered an endangered phenomenon. Deforestation, urbanization and the spread of agriculture have eliminated many stopover sites, and artificial barriers such as dams and fences have blocked migration routes for other species. These changes can artificially elevate animal densities and facilitate contact between wildlife, livestock and humans, increasing the risk that pathogens will spread across species. As co-author Han noted, "A lot of migratory species are unfairly blamed for spreading infections to humans, but there are just as many examples suggesting the opposite—that humans are responsible for creating conditions that increase disease in migratory species."

And as the climate warms, species like the monarch may no longer need to undertake the arduous migratory journey to their wintering grounds. With food resources available year-round, some species may shorten or give up their migrations altogether—prolonging their exposure to parasites in the environment, raising the rates of infection and favoring the evolution of more virulent disease strains. "Migration is a strategy that has evolved over millions of years in response to selection pressures driven by resources, predators and lethal parasitic infections—any changes to this strategy could translate to changes in disease dynamics," said Han.

"There is an urgent need for more study of pathogen dynamics in migratory species and how human activities affect those dynamics," Altizer said. The paper concludes with an outline of challenges and questions for future research. "We need to learn more in order to make decisions about the conservation and management of wildlife and to predict and mitigate the effects of future outbreaks of infectious diseases."

Viral protein mimic keeps immune system quiet
Kaposi sarcoma-associated herpesvirus produces a protein that blocks the cell's inflammatory response
In a new paper published Jan. 21 in the journal Science, a team of researchers led by Microbiology and Immunology professor Blossom Damania, PhD, has shown for the first time that the Kaposi sarcoma virus has a decoy protein that impedes a key molecule involved in the human immune response.

The work was performed in collaboration with W.R. Kenan, Jr. Distinguished Professor, Jenny Ting, PhD. First author, Sean Gregory, MS, a graduate student in UNC’s Department of Microbiology and Immunology played a critical role in this work.
The virus-produced protein, called a homolog, binds to the cellular protein that normally triggers an inflammatory response, a key immune system weapon for fighting viral infection. However, the homolog lacks a key part of the cellular protein that triggers the inflammation process. Inflammasome activation leads to the production of proinflammatory cytokines and eventual cell death.

Damania compares the homolog's action to what can happen when completing a jigsaw puzzle. "Sometimes there will be a piece that 'almost' fits into an available space, but because it's not an exact fit, leaving it there will keep you from completing the puzzle. The viral homolog gums up the works, preventing the formation of a large complex called the inflammasome, and keeping the cell's immune response from deploying."

According to Damania, a cell's response to a viral invader is to commit suicide. The cells die rather than spread the virus, which uses the cell by hijacking its genetic machinery to produce more virus. Kaposi sarcoma virus' ability to evade the body's immune system helps it lie dormant and persist in the body over a lifetime.

Both researchers are members of UNC Lineberger Comprehensive Cancer Center. Dr. Damania studies the Kaposi's sarcoma virus, which is known to cause certain types of human cancer, because it can infect cells and lie dormant without triggering cellular death. Virus-infected cells then proliferate, and can give rise to cancer.

**Study maps process used by T cells to discriminate pathogens from the body's own cells**

Researchers have for the first time mapped the complex choreography used by the immune system's T cells to recognize pathogens while avoiding attacks on the body's own cells.

"We show for the first time the important role of the co-receptor in contributing to the discrimination process that takes place in the T cell," said Cheng Zhu, a Regents professor in the Coulter Department of Biomedical Engineering at Georgia Tech and Emory University.

"This is a cooperative binding process with the co-receptor co-engaging with the T cell receptor. This cooperative binding has a synergistic effect that amplifies the action."

The resulting binding, which then triggers the body's defensive activities, is stronger than the sum of the individual binding that would result from the T cell receptor and CD8 co-receptor operating independently.

The two-step binding process, which alters the accepted model for T cell recognition, was reported Jan. 20 in the early online edition of the journal *Immunity*. The research was sponsored by the National Institutes of Health and the National Multiple Sclerosis Foundation.

Zhu and his colleagues found a time delay between when the T cell receptor engages the antigen peptide and when the CD8 co-receptor goes into action. That delay was about a second in the hundreds of contacts studied. The researchers also found that the binding feedback loop was rapid, short-lived, reversible, synergistic and peptide-discriminative.

The research used a technique known as micropipette adhesion frequency assay to study the mechanical interactions between T cells and the antigen, known as a peptide major histocompatibility complex (pMHC) – a glycoprotein.

For the study, pMHC molecules taken from a transgenic mouse were placed onto a red blood cell held by a micropipette, simulating the activity of antigen-presenting cells which normally isolate these foreign molecules and display them for recognition by T cells. A mouse T cell held by another micropipette was then placed into contact with the red blood cell for varying periods of time.

By microscopically examining adhesion between the two cells when separated, the researchers were able to determine whether binding between the T cell receptor – and the CD8 co-receptor – had occurred.
In studying the data from hundreds of contacts between different types of antigens, the researchers saw a step in the probability of binding, then a jump to a second step. By alternately blocking binding between the pMHC and the T cell receptor, and between the pMHC and the CD8, they were able to determine that the first step represented binding with the T cell receptor while the second step represented binding with the CD8.

The micropipette adhesion technique, developed by Zhu and his student, allows the study of interaction between T cell receptor molecules – of which there are as many as a million – and pMHC protein molecules. Earlier techniques had isolated the receptor molecules for study in a solution environment, but Zhu believes his two-dimensional technique provides a more realistic representation of their activity because the receptors remain on the T cell membrane.

Until now, scientists had assumed that T cell receptor and CD8 binding with the antigen took place at approximately the same time, reinforcing one another to make the intermolecular connection strong enough to trigger an immune response.

"What was surprising to us was that the two interactions do not occur simultaneously," said Zhu. "There is a delay of about one second, and we attribute that to the intracellular interactions that have to take place within the T cell before the CD8 can engage."

The research confirmed earlier findings that T cell responses to lower affinity antigen ligands were more dependent on CD 8 binding. "We confirmed this finding, but demonstrated that the major function of CD8 was to amplify recognition of the higher affinity antigen, meaning the magnitude and kinetics of the CD8 contribution favors the response to low levels of strong antigens," Zhu explained.

T cell receptors are among the most important molecules in the immune system because of their role in recognizing the antigens on target cells. The receptors also must distinguish those threats from the body's own cells to avoid triggering an unwanted immune response.

For the future, Zhu would like to clarify what advantages the two-step process provides when a tiny amount of "non-self" antigen peptides are presented together with a large amount of "self" peptides, and attempt to understand how the T cells seek out interactions with foreign antigens.

"This new study adds significantly to the understanding of how T cell receptors and associated molecules differentiate the antigens of the body's own cells from those of an invader," Zhu added. "It may be that this co-receptor plays a role in helping discriminate viruses that have mutated and are no longer a direct match to what the T cell is looking for. That's another hypothesis we hope to study."

**Big snip heads for big debate, circumcision is rising in private procedures say doctors**

From: *The Daily Telegraph*
January 20, 2011 10:57PM

Circumcisions are on the rise again say doctors as debate about the benefits of the procedure continue.

MORE Australian parents are choosing to have their newborn sons circumcised, reigniting debate in the medical community about whether the procedure is necessary.

The practice was banned in NSW public hospitals five years ago and doctors have seen a significant increase in demand for circumcisions to be performed in private, reported *The Daily Telegraph*.

The world-renowned Centers for Disease Control and Prevention in the US is preparing a policy on the issue which is expected to support mandatory circumcision.

However the Royal Australasian College of Physicians recently announced it does not support routine infant circumcision, despite a growing body of evidence that it helps prevent sexually transmitted infections such as HIV.

Doctors that perform the procedure in Sydney medical clinics are seeing up to 40 newborn babies a week, with the number rising each year.

Start of sidebar.

"I am seeing dozens and dozens a week," obstetrician Dr Norman Bluementhal said.

"It started to change about two years ago after there was adverse publicity but now people are going back to it." Circumcision, which began declining in popularity after the 1970s, costs about $800.
Medicare figures show the rate of the procedures in NSW is rising, with 18 per cent of boys born in 2009 circumcised compared to just 13 per cent a decade ago.

A group of Sydney doctors is criticising the anti-circumcision stance taken by the medical colleges and hospitals, believing parents are putting their sons at risk by not having them circumcised.

Paediatric surgeon Dr Anthony Dilley conducts up to 40 circumcisions a week and said parents were now more open to the idea.

"Over the last 10 years there’s been lots of good research showing there’s good reasons to have circumcision," he said.

A recent paper by a group of Sydney-based doctors, including Alex Wodak from St Vincent's Hospital and Professor Brian Morris from Sydney University's school of medicine, said circumcision was a long-term strategy to reduce HIV.

Circumcision is also widely accepted in some cultures for religious reasons and is seen as a rite of religious passage in the Jewish community.

Dani and Toni Zaidel, of Vaucluse, said their twin boys Jacob and Benjamin, born seven weeks ago, were already circumcised and they had celebrated the occasion.

"It was the proudest day of our lives," Mr Zaidel said.

But College of Physicians paediatrician Dr David Forbes said the college would not be swayed on the issue.

"We may never change the view. It's hard to say when or if there will be [enough] evidence [to support it]," he said.

**How Better ARV Prices Were Won**

By Laura Lopez Gonzalez

**JOHANNESBURG, Jan 21, 2011 (IPS)—**South Africa’s recently-awarded tender for antiretroviral drugs halved drug costs for the world’s largest ARV programme. Driven by a better-prepared and more aggressive government, the deal may stand up to criticism better than initially thought.

In a country with an estimated HIV prevalence rate of about 18 percent, more than a million South Africans are currently on ARVs.

South Africa will save an estimated 685 million dollars over the two-year life of the new tender. The deal was nonetheless criticised for an alleged lack of transparency, and for possibly preventing even greater savings by locking in prices for drugs that could become yet cheaper.

Generally, the agreement was praised, although it could prove a difficult example for other countries to follow.

**How the deal was done**

While increased competition from new manufacturers of generic medicines alone could have reduced drug prices, the South African government took steps to ensure tender prices were internationally competitive, partnering with CHAI to set out target prices prior to issuing the tender – a first for the country.

Bidding companies were also required to submit detailed breakdowns of drug costs, listing the proportion of costs associated with production—from active ingredient purchases and drug formulation to shipping.

"What South Africa tried to do was get a sense of the cost of actually manufacturing the drug and what might be a reasonable profit margin," says Brenda Waning, Coordinator of Market Dynamics for UNITAID, the United Nations drug-funding agency. "It’s very difficult figure for companies to release—it’s like their best kept secret."

It’s not clear how accurate the information provided is, but by comparing the submissions of a number of manufacturers, it’s possible to judge how valid the figures are, she adds.

These cost breakdowns may prove crucial later on, should either drug companies or the government try to argue for a change in prices mid-tender.

The tender allows companies to apply to raise drug prices mid-tender, but firms will have to justify these increases. Having an initial benchmark of cost components will allow government to better evaluate these claims, says Vishal Brijlal, the Clinton Health Access Initiative's (CHAI) South Africa country director. The government is under no obligation to accept proposed price hikes, he adds.
Newly introduced clauses like these may be in response to past abuses by drug suppliers, who have tried to claim for costs, such as currency fluctuations, that are not only part of ordinary business costs but often offset by insurance.

**Room for improvement?**
Meanwhile, a quarterly review of the prices for active pharmaceutical ingredients in antiretrovirals, which comprise up to 70 percent of some drugs’ costs, will allow government to identify any change in the cost of manufacturing them. While government may then request price reductions from tender prices suppliers, it remains unclear whether firms will be obligated to reduce these prices.

According to Brijlal, suppliers will be mandated to lower their prices. Jonathan Berger, a senior researcher for South African human rights organisation Section 27, disagrees.

"My understanding is that the department says there is a provision to renegotiate price," Berger says. "But there is no obligation for companies to accept that. It’s meaningless—that was the biggest problem for the tender."

The Department of Health was not available for comment.

For Waning, South Africa’s new tender represents a shift in international purchasing power, away from donors and towards large national buyers of essential medicines like India, China and South Africa, which funds 60 percent of its treatment programme.

"As countries assume more responsibility for treatment of patients and donors assume less, countries are having more of a say over who’s who in terms of pharmaceutical suppliers," she says.

South Africa’s massive purchasing power and large share of the global market may make civil society criticisms about the tender’s lack of transparency more important.

In a December 2010 statement, Section 27 and the advocacy group Treatment Action Campaign called on government to detail how points were awarded in future tenders.

"We don’t know how points were worked out... competitors can’t tell whether or not the tender was correctly awarded," Berger says. "Other competitors have a right to know how points were allocated and why they didn’t win."

According to Brijlal, competitors could deduce points earned from public documents but he admits it would be difficult.

**What the future holds**
But South Africa’s ability to negotiate cheaper drugs mid-tender will likely only apply to possible savings on newer ARVs such as tenofovir, where advances in formulation, generic competition or economies of scale could bring down prices, according to Andy Gray, a senior lecturer at the department of therapeutics and medicines management at South Africa’s University of KwaZulu-Natal.

Prices for older drugs, like stavudine, are unlikely to show more than single digit percentage drop in coming years, and prices for these drugs have likely gone as low as they can go, says Brijlal.

While Waning warns that international pressure for cheaper drugs has to be balanced against concerns that ARV producers will lose interest in the market, Gray says the nature of the AIDS pandemic continues to make it an attractive venture for companies – and opens up the possibility for potentially cost-saving advancements.

As HIV continues to mutate, patients may develop resistance to first-line drugs and will need new drug regimens.

"Even in high priced markets like the US, patients are requiring rescue regimens because of resistance and that’s still sufficient to keep some firms in research and development," Gray says. "What makes it easier [to attract companies], is that, as opposed to conditions like hypertension, HIV requires a lifelong treatment."

With about 14 percent of patients attending South African clinics run by the international medical charity, Medicines Sans Frontiers, developed resistance to first line drugs within five years of starting ARVs; a quarter of those patients needed third line drugs just two years later.

While advancements in ARVs and markets may make it cheaper for countries like South Africa to access the drugs, Brijlal says countries sourcing their own ARVs need to do their research to capitalise on better prices but admits that capacity remains weak.

"With the movements among donors to post drug prices, there’s no reason that countries can’t be prepared when they negotiate and that’s the most powerful tool," Waning said.
New Hope for Hepatitis C, an Often Hidden Disease
Associated Press, (01.17.2011) Lauran Neergaard

2011 is shaping up to be a landmark year for hepatitis C treatment. The Food and Drug Administration this summer could decide on whether to approve two drugs that are the first to directly target the hepatitis C virus (HCV)—Merck & Co.’s boceprevir and Vertex Pharmaceutical’s telaprevir. Taken in combination with standard treatment, the drugs boost the cure rate for the most common form of the virus from 40 percent to as high as 75 percent. And they allow some patients to cut treatment time in half, lessening exposure to grueling side effects.

Experts draw comparisons to the 1990s when potent combination therapies emerged to treat HIV/AIDS. With a treatment revolution on the horizon, federal health officials are considering recommending routine HCV screening for baby boomers, an at-risk group.

“We’re entering a whole new era of therapy,” said Dr. John Ward, director of the Division of Viral Hepatitis at CDC’s National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention. “We really want to begin that clarion call for action for this population who’s at risk.”

Some 3.2 million Americans have chronic HCV. Two-thirds of those with the infection are thought to be baby boomers who have harbored the virus since they were young. Though new US infections have dropped dramatically, HCV’s toll is rising because it can take two or three decades for the infection to cause damage. HCV kills about 12,000 US patients annually, a number expected to triple within 20 years.

CDC is studying the feasibility of one-time HCV screening among baby boomers at four hospitals in New York, Detroit, Houston, and Birmingham, Ala. The agency plans to release new guidelines next year.

Chechnya Says Couples Must Be HIV-Negative to Marry
Reuters, (01.18.2011) Amie Ferris-Rotman

Any couples planning to marry in Muslim Chechnya must prove they are not infected with HIV, the region’s spiritual leaders declared this week.

“Any potential bride or groom is obliged to receive a medical certificate proving they are HIV-negative,” according to a statement by the Chechen mufti, or professional jurist who interprets Muslim law. An imam can only approve of a marriage once that certificate is obtained. “Only an official representative from the republic’s clergymen has that right,” the statement added.

The order follows a demand last year that all eateries cease operations during the holy month of Ramadan and the call for armed men to harass women who do not wear headscarves. The mufti’s requirements carry no legal weight but are generally followed because he is a respected spiritual leader.

However, activists and some residents in the volatile region are outraged by the new requirement.

“This is, of course, not within Russian law,” said Minkail Ezhiev, a human rights activist and founder of the Chechen Civil Society Forum. “We wish human rights were taken into account here.”

Russia is in the midst of a serious heroin crisis, which could lead to an explosion of HIV/AIDS cases. The UN estimates at least 1 million Russians are HIV-positive, though Chechnya has been largely spared by the epidemic.

Barriers to Implementation of Isoniazid Preventive Therapy in HIV Clinics: A Qualitative Study
AIDS Vol. 24; Suppl. 5: P. S45-S48, (11..2010) Rebecca Lester; Robin Hamilton; Salome Charalambous; Thobeka Dwdwa; Clare Chandler; Gavin J. Churchyard; Alison D. Grant

Though isoniazid preventive therapy (IPT) has been shown to reduce TB incidence among people with HIV, and is recommended in an HIV care program in Gauteng province, its implementation there is low, the study authors noted. Based on in-depth interviews and a focus group discussion, they described barriers to IPT implementation in the donor-funded program as well as provider and patient perspectives on IPT.

The team interviewed 22 clinic staff and 20 patients from 10 purposively selected HIV clinics in the program. Staff members were surveyed about their knowledge of and experience with IPT and about barriers to its implementation. Patients were asked their opinions about IPT.

The primary barriers to IPT were lack of knowledge and experience, staff reported. Prescribers were unaware of IPT benefits and unclear about guidelines. Other barriers included the belief that TB screening tools are inaccurate in HIV patients and the need to refer patients to separate clinics to conduct TB screenings. None of the patients had ever heard of IPT.
“Barriers to the widespread use of IPT primarily derived from health care workers, in particular lack of experience among physicians,” the authors concluded. “In addition to overcoming operational barriers, a change in health care worker perception is needed if IPT is to be widely used; we suggest local clinical opinion leaders could help achieve this.”

**Rotavirus Vaccine Significantly Cuts Child Hospitalizations, Study Says**
Developing and developed countries that require children to be vaccinated against rotavirus “have significantly reduced the number of children admitted to hospitals with the disease, a report showed on Thursday,” Reuters reports (Kelland, 1/20).

Study findings, published in a special supplement to the Pediatric Infectious Disease Journal, note significant declines "in the number of children hospitalized due to rotavirus in countries that include rotavirus vaccines as part of their routine immunization programs," according to a press release issued by CDC, the GAVI Alliance, PAHO and PATH (1/20).

"Since introducing the vaccine in 2006, the United States has seen a 58 to 86 percent reduction in such hospitalizations over three years, said the study. In Australia, there was a bigger decline of 89 to 94 percent since 2007, and El Salvador saw a 69 to 81 percent drop in hospital visits among children under five. Mexico, which introduced the vaccine in 2007, saw a 40 percent drop in diarrhea-related hospitalizations in 2009," Agence France-Presse reports (1/20).

The studies "also show large reductions in rotavirus disease among older, unvaccinated children, suggesting that vaccination of babies may also limit the overall amount of virus transmission, giving what is known as 'herd immunity,'" according to Reuters. "In both the developed and developing worlds, we see a rapid and impressive reduction in rotavirus infections following the roll-out of vaccine," said John Wecker, director of the vaccine access and delivery global program at PATH. He said the findings should encourage donors and lawmakers to implement the 2009 WHO recommendation, which called for all countries to develop national rotavirus vaccine programs (1/20).

The CDC's Anne Schuchat praised the vaccine for being "safe, effective and most importantly, saving children's lives," AFP writes. "Unfortunately, too many children around the world get severely ill or die from this preventable disease. We must continue to expand our efforts to ensure that children around the world have access to these vaccines," she said (1/20).

**Red Blood Cell Hormone Modulates the Immune System**
ScienceDaily (Jan. 20, 2011) — New research reveals that a hormone best known for stimulating the production of red blood cells can modulate the immune response. The study, published in the Jan. 27 issue of the journal Immunity, finds that erythropoietin (EPO) has contrasting influences on infectious and inflammatory diseases and may be useful in the design of new therapeutic strategies.

EPO is a cytokine hormone that stimulates the production of red blood cells by acting at EPO receptors (EPORs) on red blood cell precursors. Interestingly, other cell types also express EPORs. "It is clear that EPORs are present on immune cells, but the function of these receptors was completely unknown," says senior study author Dr. Guenter Weiss from Innsbruck Medical University in Austria. "We hypothesized that EPO might be able to modulate the immune system and could be of clinical relevance in certain diseases."

After showing that EPO inhibited induction of key pro-inflammatory genes, Dr. Weiss and colleagues examined the role of EPO-modulated immune cells in two mouse models of disease: systemic infection with Salmonella bacteria and chemically induced inflammation of the colon (colitis).

In mice infected with Salmonella, EPO treatment was associated with reduced survival and impaired ability to clear the pathogen, neutralization of EPO production in the body promoted Salmonella elimination. This suggests that EPO reduces the ability of the immune system to fight off a systemic infection with intracellular bacteria such as Salmonella.

The researchers went on to show that in contrast to bacterial infection, EPO had a beneficial effect on the severity of colitis. EPO decreased the production of nuclear factor (NF)-κB, a protein that is critical for inflammation and thereby reduced the formation of cytokines such as tumor necrosis factor alpha which are centrally involved in the pathogenesis of autoimmune colitis. This suggests that EPO may exert beneficial effects in non-infectious inflammatory diseases.

"Our results provide novel evidence that EPO acts as a potent anti-inflammatory immune modulator by specifically targeting (NF)-κB-driven inflammatory pathways," concludes Manfred Nairz, first author of the paper. "Although high dose EPO treatment in humans may lead to a dangerous excess of red blood
cells, EPO derivatives that do not influence red blood cell production have been developed and these could possibly serve as valuable therapeutic tools in treatment of pathologic inflammation."

**Journal Reference:**

**Genetic Variety of Virus Causing AIDS as a Time Indicator**
ScienceDaily (Jan. 21, 2011) — Researchers of the Swiss HIV Cohort Study have identified a simple method to establish when a patient contracted the virus causing AIDS. The time of infection can be of importance for the treatment of the illness and it contributes to the understanding of the course of the epidemic.

Medical doctors rarely know when a patient contracted HIV. The exact point in time can only be established in the first eight weeks after infection—during the so called acute phase. If the HIV test is taken later, it remains unclear if the infection took place three months or ten years ago. But this is about to change as researchers supported by the Swiss National Science Foundation (SNSF) have discovered a simple method to determine the approximate time of infection.

**Relevant to understanding the spread of the illness**
According to Huldrych Günthard from the university hospital in Zurich, information regarding the time of infection is beneficial in many ways. It allows doctors to establish how quick the illness is progressing and to determine the start of treatment accordingly. It will also inform epidemiological studies interested in how the disease is spreading.

In collaboration with colleagues from the ETH Zurich, researchers of the Swiss HIV Cohort Study analysed data that is obtained in routine resistance tests. These tests examine the genetics of the virus to establish its resistance to drugs. If a patient carries a variety of HIV strains, the test reveals ambiguous results with regard to certain points in the sequences of the virus' genetic code.

**By-product of resistance testing**
"For a long time, the ambiguous results of the viral sequencing were considered a by-product of the test," says Günthard. "We wondered if they were an indicator of the variety of viruses in the blood." Viral variety is a result of reproduction and evolution in the body, it increases with time and the ambiguity could therefore be an indicator for the time that has passed since infection. Günthard and his team tested this assumption by comparing the drug resistance data with an existing rudimentary method to calculate the time of infection. Additionally there are patients who know the exact time of HIV infection: e.g. patients who took the test during the acute phase or patients who took tests before and after the infection.

The study, that has now been published in the journal *Clinical Infectious Diseases,* was able to show that the proportion of ambiguous sequences is indeed increasing regularly during the first eight years after infection, afterwards the increase slows down. At the moment the new method is still too imprecise to establish the exact time of infection but the researchers were able to define a threshold level that indicates with 99 percent certainty if an infection happened more than a year ago.

**Journal Reference:**

**Experts Reveal Alarming Figures: Doctors See Huge Increase in Sexual Diseases**
*Sunday Life (Belfast Telegraph),* (01.23.2011) Gail Henderson
A new documentary, set to broadcast on Jan. 25, offers a behind-the-scenes look at the Royal Victoria Hospital's Genito-Urinary Medicine (GUM) clinic and details the rise in STDs in recent years in Northern Ireland.

According to data presented in “The Pox Doc,” syphilis is up 142 percent, genital herpes 7 percent, genital warts 11 percent, chlamydia 12 percent, and gonorrhea 31 percent. The clinic treats more than 10,000 patients annually.

Internationally renowned sexual health expert Dr. Raymond Maw has worked at GUM for nearly 35 years. Despite a massive increase in STD infections and patients, Northern Ireland remains by far the worst-funded GUM clinic in the UK, he said.
Also featured is Dr. Carol Emerson, who conducts outreach for high-risk males, visiting bathhouses and setting up a clinic at Belfast’s Gay Pride festival. “Almost 50 percent of men we have seen have never had an HIV test before,” she said. “That’s shocking.”

“The Pox Doc” will run on Tuesday on BBC One Northern Ireland; check local listings for times.

**Vaccination Campaigns To Stop Yellow Fever Spread Get Underway In E. Africa**

Individuals traveling across East Africa on Friday were ordered to begin receiving mandatory yellow fever vaccines in an effort "to contain an outbreak of the disease in Uganda," which has sickened an estimated 190 people, resulting in 48 deaths as of Dec. 30, 2010, the Citizen reports (Ubwani, 1/22).

The vaccination plan was announced following a meeting of East African Community (EAC) partner states held to review the "status of yellow fever in the EAC partner states and consider joint cross-border and national mass supplemental immunisation campaigns," Guardian/IPP Media reports in a piece that looks at how the countries hope to also target an immunization campaign for children living in the region. The piece examines how shortages in yellow fever vaccines may delay a start to the campaign and how the governments are working together to increase the amount of yellow fever vaccines available (Philemon, 1/24).

According to the Citizen, Hadji Mponda, Tanzania's minister for health and social welfare, "told reporters that all ... EAC partner states have now agreed that vaccination against the disease must be compulsory for those crossing national borders" and that vaccine centers were being set up at border posts. Mponda also said he knew of no known reported cases of yellow fever in Tanzania to date, yet he expressed concerns about the quantity of yellow fever vaccines available for distribution.

Also "[s]peaking at the meeting, EAC deputy secretary general Jean Claude Nsengiyumva said the yellow fever outbreak was of major concern to the region," the newspaper writes. Beth Mugo, Kenya's minister for Health and Sanitation, also speaking at the meeting, said she too was unsure of the presence of yellow fever in Kenya (Ubwani, 1/22).

According to an East African Community press release, "[o]ther partner states have not reported any case of yellow fever outbreak. The ministers from Rwanda and Burundi informed the meeting that last time yellow fever occurred in their respectively countries was in the 1950's but mitigating measures have been put in place following the reported cases in Uganda" (1/21).

Guardian/IPP Media examines how shortages in yellow fever vaccines may delay a start to the campaign and how the governments are working together to increase the amount of yellow fever vaccines available (1/24).

Meanwhile, UNICEF "is kicking off a yellow fever vaccination campaign in Ivory Coast despite growing instability and hostility to U.N. staff following a disputed presidential election in November," VOA News reports. Health workers hope to immunize "more than 800,000 adults and children in north-central Ivory Coast against yellow fever over the next week," across four rural districts "where 66 cases of the mosquito-borne illness have been recorded since November, including 25 deaths," according to the news service.

Despite delays to the vaccination campaign due to the "tense political gridlock that has gripped the country since a November 28 presidential poll," Louis Vigneault-Dubois, UNICEF spokesperson in the Ivory Coast, spoke about the urgent need to carry out the campaign immediately. "Now it has reached a point where it is urgent to vaccinate the people, to stop the epidemic in the four districts that are concerned by the current campaign and to make sure that the disease does not spread further beyond the four districts that are concerned," said Vigneault-Dubois.

The article details the political climate in the Ivory Coast and notes how security could be an issue for health workers trying to administer yellow fever vaccines (Look, 1/21).

**Unexpected Find Opens Up New Front in Effort to Stop HIV**

ScienceDaily (Jan. 24, 2011) — HIV adapts in a surprising way to survive and thrive in its hiding spot within the human immune system, scientists have learned. While the finding helps explain why HIV remains such a formidable foe after three decades of research—more than 30 million people worldwide are infected with HIV—it also offers scientists a new, unexpected way to try to stop the virus.

The work by researchers at the University of Rochester Medical Center and Emory University was published Dec. 10 in the Journal of Biological Chemistry.

It’s thanks largely to its ability to hide out in the body that HIV is able to survive for decades and ultimately win out against the body’s relentless immune assault. One of the virus’s favorite hiding spots is
an immune cell called a macrophage, whose job is to chew up and destroy foreign invaders and cellular debris.

For more than 15 years, Baek Kim, Ph.D., has been fascinated by HIV's ability to take cover in a cell whose very job is to kill foreign cells. In the last couple of years Kim, professor of Microbiology and Immunology at the University of Rochester Medical Center, has teamed with Emory scientist Raymond F. Schinazi, Ph.D., D.Sc., director of the Laboratory of Biochemical Pharmacology at Emory's Center for AIDS Research, to test whether the virus is somehow able to sidestep its usual way of replicating when it's in the macrophage.

The pair found that when HIV faces a shortage of the molecular machinery needed to copy itself within the macrophage, the virus adapts by bypassing one of the molecules it usually uses and instead tapping another molecule that is available.

Normally, the virus uses dNTP (deoxynucleoside triphosphate, the building blocks for making the viral genetic machinery) to get the job done, but dNTP is hardly present in macrophages—macrophages don't need it, since they don't replicate. But macrophages do have high levels of a closely related molecule called rNTP (ribonucleoside triphosphate), which is more versatile and is used in cells in a variety of ways. The team found that HIV uses primarily rNTP instead of dNTP to replicate inside macrophages.

"The virus would normally just use dNTP, but it's simply not available in great quantities in the macrophage. So HIV begins to use rNTP, which is quite similar from a chemical perspective. This is a surprise," said Kim. "The virus just wants to finish replicating, and it will utilize any resource it can to do so."

When the team blocked the ability of the virus to interact with rNTP, HIV's ability to replicate in macrophages was slashed by more than 90 percent.

The work opens up a new front in the battle against HIV. Current drugs generally target dNTP, not rNTP, and take aim at the infection in immune cells known at CD4+ T cells. The new research opens up the possibility of targeting the virus in macrophages—where the virus is out of reach of most of today's drugs.

"The first cells that HIV infects in the genital tract are non-dividing target cell types such as macrophages and resting T cells" said Kim. "Current drugs were developed to be effective only when the infection has already moved beyond these cells. Perhaps we can use this information to help create a microbicide to stop the virus or limit its activity much earlier."

Kim notes that a compound that targets rNTP already exists. Cordycepin in an experimental compound, derived from wild mushrooms, that is currently being tested as an anti-cancer drug. The team plans to test similar compounds for anti-HIV activity.

"This significant breakthrough was unappreciated prior to our paper. We are now exploiting new anti-HIV drugs jointly based on this novel approach that are essentially not toxic and that can be used to treat and prevent HIV infections," said Schinazi, who has developed several of the drugs currently used to treat HIV patients.

**Journal Reference:**

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**South Africa’s population to shrink after 2030**

**Estimates show that from 2030 onwards, South Africa will have a decreasing population.** This is according to the 2009/10 South Africa Survey published by the South African Institute of Race Relations in Johannesburg this week.

Between 2010 and 2030, South Africa’s population will grow, although at a decreasing rate each year. By 2030 South Africa’s population will be 53.81 million. The population will then decrease to 53.74 million by 2035, and to 53.28 million by 2040, according to data from the Institute of Futures Research at the University of Stellenbosch cited in the Survey.

One of the main reasons for this is the long term impact of HIV/AIDS.

In South Africa, the number of deaths in a year is making up an increasingly higher proportion of the number of births. In 1985, deaths were 25% of births. This was expected by the Actuarial Society of South Africa to increase to 87% of births by 2021.

Thuthukani Ndebele, a researcher at the Institute, said, ‘If this trend continues, there will soon be more deaths than births in South Africa. It is evident that the HIV/AIDS pandemic has resulted in an
increasing number of deaths. These deaths are mostly among people in the child-bearing age group, which will result in decreasing numbers of births.’

However, a lower fertility rate will also contribute to population shrinkage. Between 2001 and 2010, South Africa’s fertility rate decreased from 2.86 to 2.38 births per woman.

By 2040, the fertility rate will have dropped to 1.98 births per woman. This is lower than the replacement rate of 2.1 births per woman, which is needed for the population to reproduce itself.

Ndebele said, ‘Lower fertility rates are related to an increase in access to education and contraceptives, which results in women having fewer children.

‘A combination of increasing deaths as a result of the HIV/AIDS pandemic, as well as lower fertility rates will result in population shrinkage after 2030. This can be positive as there will be less strain on resources in South Africa. However, it will also be negative, as there will be fewer people to contribute to the economy and its internal consumer markets.’

Special report: In Russia, a glut of heroin and denial **** (long)

(Reuters)—In her one-room flat, as a small shelf of porcelain cats looks on and the smell of mold hangs in the air, Zoya pulls down the left shoulder of her black blouse and readies herself for her next hit.

A friend and ex-addict uses a lighter to heat a dark, pebble-like lump of Afghan heroin in a tiny glass jar, mixes it with filtered water and injects it into Zoya’s shoulder. The 44-year-old widow is a wreck: HIV-positive, overweight and diabetic. After 12 years of dealing and drug abuse, the veins in her forearms and feet are covered in bloody scabs and abscesses, too weak and sore to take fresh injections.

Crimson-dyed hair frames her bloated face, which is made up to match a hot pink manicure. As the syrupy brown mixture enters her system, Zoya’s eyes glass over and she ponders her fate and that of her country.

"There are a lot of us. What do they (the government) want to do? Kill us?" she says. "They want to gather us together and drown us? I worry for tomorrow’s generation."

If Zoya is anything to go by, today’s Russians are hardly flourishing. Russia has one of the world’s biggest heroin problems, with up to three million addicts according to local non-governmental organizations. Twenty one percent of the 375 tons of heroin produced from Afghanistan’s opium fields now finds its way through central Asia into Russia, according the United Nations. (By contrast, China, with nine times more people, consumes just 13 percent.) The Russian government estimates its citizens bought $17 billion worth of street-traded heroin last year—about seven billion doses. The addiction kills at least 30,000 Russians a year, which is a third of the world’s total heroin-related deaths, adding to pressures on the country’s already shrinking population.

So grave is the problem that President Dmitry Medvedev last year branded heroin a threat to national security.

That’s one reason why last October, 21 years after the end of the decade-long Soviet war in Afghanistan, Russian troops joined forces with U.S. soldiers for a joint drug raid on four Afghan labs. The operation, which destroyed nearly a ton of heroin, was hailed a success and the Cold War foes said they would like to see more such operations in Afghanistan, which is responsible for 90 percent of the world’s heroin production.

At home, though, Russia has been far less active in tackling the problem. Critics go as far as to accuse Moscow of wilfully neglecting its citizens and thereby fuelling what the World Health Organization says is one of the fastest growing HIV/AIDS epidemics in the world.

Unlike most countries around the world, Russia refuses to finance harm reduction programs such as needle exchanges, or to legalize methadone. Over the past few months, Moscow has decided to discontinue the work of foreign donors and NGOs with heroin addicts. It even recently blamed foreign groups for worsening the country’s HIV epidemic.

Health experts and drug addicts alike point to official inaction as the real culprit. It’s as if Moscow has misinterpreted the old U.S. anti-drugs slogan “Just Say No” and turned its back on the crisis. “My government does nothing for me. I am no longer a person in this society,” says Zoya, who lives in Tver, a drab city of half a million just off the Moscow-St Petersburg highway, and whose husband, also an addict, died from AIDS several years ago.

Anya Sarang from the Andrey Rylkov Foundation for Health and Social Justice, a small UN-funded Russian organization set up in June 2009, says Russia is failing its people. "For the main groups prone to the disease—drug users, sex workers, migrants—there is absolutely nothing for them,” says Sarang.
The Proud Bear

Russian officials have a long history of denying crises. From the Soviet government’s refusal to help during the famine of the 1920s to its delay in responding to the 1986 Chernobyl nuclear accident, responses from the top have often mixed disregard and cover-up. During last August’s heat wave, as peat fires and acrid smoke killed hundreds, officials kept silent on the wider health effects of the smoke for weeks.

One of the reasons for the rush to denial lies in the national psyche. Russia is a deeply patriotic country, with a long history of strong governments far removed from the everyday concerns of ordinary citizens. After the humiliating collapse of the Soviet Union 20 years ago and the calamity and poverty that followed, the strongman rule of Vladimir Putin (former president and current Prime Minister) has allowed the Russian bear to flex its muscles on the international stage again.

But while Moscow crows about hosting such high-profile sporting events as the Winter Olympics and soccer World Cup, it ignores daily reality, says health worker Sarang. "Russia is trying to preserve a certain political image, showing that everything is fine," she says. "This has shown to be nothing more than a lie."

Most Russians see the truth all around them. Zoya’s story is repeated so often across the country’s nine time zones that the reality is hard to ignore. Even the government estimates there are 1.8 million heroin users; activists and doctors put the number closer to 3 million, and in a study last June, the United Nations put it at 2.34 million or 1.64 percent of Russia’s population. That’s the world’s third highest heroin abuse rate in per capita terms after Afghanistan and Iran. In absolute numbers, the UN says, Russia is number one.

Heroin was virtually unheard-of during the Soviet era, but is now easy to buy in any city in the country. In Tver, a medium-sized city with relatively little industry and few job prospects for the young, the detritus of addiction—used syringes, needles—litters the streets. Deals are a regular sight on street corners.

Russia’s anti-drugs tsar, Viktor Ivanov, who heads the Federal Drug Control Service—a powerful government body given to U.S.-style rhetoric about the ‘War on Drugs’—blames the country’s porous Central Asian borders for the heroin hunger.

"Unfortunately, in 1991 we suddenly found ourselves without borders," Ivanov told reporters in December, referring to the collapse of the Soviet Union.

Ex-Soviet Tajikistan, which borders Afghanistan and is one of the world’s poorest countries, has long been a haven for drug smuggling out of Afghanistan, where the Tajiks have ethnic ties. From there the heroin flows through Kyrgyzstan and Kazakhstan and into Russia.

Intertwined With AIDS

The drug problem has now become an AIDS problem. Officially, Russia has 520,000 registered HIV-positive people. The UN and local NGOs say there are probably closer to a million, maybe even more. HIV/AIDS has spread rapidly over the past decade, especially among drug users who regularly share dirty needles. The government estimates around a third of all drug users in Russia are HIV-positive; and international and Russian health experts worry the disease is beginning to spread to the general population through heterosexual sex.

The biggest problem, say health experts, is the government’s refusal to address Russia’s drug addiction. The lack of official intervention is remarkable. There are currently just 70 needle exchange and distribution programs in Russia, reaching a mere 7 percent of heroin addicts according to the London-based International Harm Reduction Association (IHRA). In terms of needle exchanges, "Russia is not even scratching the surface," says Rick Lines, executive director of the IHRA.

All the programs are run with foreign funding. Government support: nil. It’s not as if the government is powerless. In the one area of the HIV/AIDS epidemic where it is active—mother-to-child transmission—it has reduced transmission rates to almost zero.

Highway AIDS Test

In the face of government inaction, grassroots groups have mushroomed across the country.

Outside Tver, Yuri Suring parks his beat-up black Toyota at a truck stop along the Moscow-Saint Petersburg highway every night. There, between 7 pm and 4 am, he surreptitiously doles out clean needles and condoms to prostitutes, many of whom work to support their drug addictions. "If I were not here, where would these girls go? Who would help them? No one," Surin says as a trio of prostitutes in knee-high boots and bomber jackets approaches the car.
Surin’s organization, We And AIDS, consists of himself, a second outreach worker and a driver. The supplies he hands out every night and the kits he uses to test women come, he says, from sympathetic doctors and western groups who want to help.

On a cold night in November, 20-year-old prostitute Olga slips into Surin’s car for an AIDS test. Surin rubs a two-inch indicator on her gums and inserts it into a small plastic tray while Olga nervously smokes a cigarette and shakes her black-bobbed head from side to side in anger at her fate, her gold leaf-shaped earrings swaying.

After studying the result—negative—the prostitute flings the indicator out of the car window and then hops across the gravel into a truck cabin where customers—two large middle-aged truckers—are waiting.

The Health Ministry says it spent 10 billion roubles ($320.5 million) on HIV/AIDS testing and treatment—mostly antiretroviral drugs—in 2010. But activists and health experts say this amount compares badly with other countries in the G20 and sufferers are routinely ignored.

In a 2010 report, the World Health Organization said just a fifth of Russians who needed AIDS drugs were receiving them. South Africa, which has the biggest HIV-positive population in the world—and whose government until recently was criticised as being in denial on AIDS—gives AIDS drugs at almost twice that rate.

"Appeals, trials and public action—nothing works," says Alexandra Volgina, head of The Candle Foundation for HIV-positive people, a non-governmental organisation in Saint Petersburg. When asked why so many sick Russians lack access to AIDS drugs, the health ministry’s spokesman responds: "The amount spent was deemed sufficient."

**Population Problems**

Russians usually blame alcohol for their health problems. Official data shows the average Russian drinks 18 liters (38 pints) of pure alcohol every year, compared with 14 liters in France and eight in the United States.

Official campaigns against drinking have been pursued sporadically since Tsarist times, usually with little success. In September last year Russia banned night-time sales of heavy alcohol, following on from a proposal to double the minimum price of vodka over the next two years in an effort to curb drinking.

"They (the government) are nicer to alcoholics than they are to us," says 32-year-old heroin addict and Tver resident Valera, whose scaly hands and face are covered in bright pink scabs from a decade of use. Like many drug addicts, Valera does not work and refuses to say how he funds his $300-a-day habit.

The Geneva-based International Aids Society warns that if Moscow continues to take no measures, the number of new HIV infections in Russia is likely to grow by 5-10 percent a year, pushing the problem to "an endemic level", according to IAS president Elly Katabira: the rate will stay constant even without any additional infections from outside the country.

That would hit Russia's already dwindling population—recently called a "demographic crisis" by President Medvedev. Heavy smoking, alcoholism, pollution, poverty, low birth rates in the years after the fall of Communism, as well as HIV/AIDS underpin UN projections that the population will shrink to 116 million by 2050 from 142 million now. Moscow—which now gives money to mothers bearing two or more children—targets a population of around 145 million by 2025, but concedes that it could fall to as low as 127 million by 2031.

**Desperate For Methadone**

If one thing appals foreign health officials and activists more than anything else about Moscow's response to its heroin problem, it's the ban on methadone. The WHO regards methadone as essential in combating heroin dependence, but in Russia anyone caught using it or distributing it can face up to 20 years in prison—ashar the sentence as that for heroin.

Called a replacement drug, methadone is taken by mouth—so reduces the risk of HIV infection by using shared needles—and is used around the world to treat opiate addiction. Russia is one of just three countries in Eastern Europe and Central Asia to ban the drug, alongside Turkmenistan and Uzbekistan, where heroin consumption is relatively low. China, which has over one million registered heroin addicts, with unofficial estimates running several times that, has more than 680 methadone sites.

Methadone is a potent synthetic opiate in its own right, but it can eliminate the agonizing withdrawal symptoms that addicts experience when they quit heroin. Its main advantages are that it has to come from a health-care source, in controlled doses and without needles. That gives addicts some chance, over months or sometimes years, to go clean for good.

In Tver, Yuri Ivanov, a doctor and the deputy head of the state-run Tver Regional Narcology Clinic, is dumbfounded by the ban. "Why do civil servants limit me from doing my work?" he asks in his dimly lit office in the crumbling grey clinic, which sits off an unpaved muddy lane in the center of the city. "All that
they are trying to do is the opposite of what we need. It is hard for me to understand... The situation is going backward. When there is no real medicine, they go right back to drugs."

Ivanov sometimes resorts to giving his patients tropicamide, a drug used by eye surgeons to dilate the pupils and which has a similar effect to heroin.

Addicts talk of their rare encounters with methadone users with a sense of wonder and even magic. "All of us know about this drug methadone and all of us want it. People come through who have done it and we can instantly see how much brighter and better they live," says Tver addict Valera in jittery sentences, high after shooting up twice by midday, in an interview in the back of his tobacco-stained car.

But Moscow won't be swayed. "The medicine has become more dangerous than the illness. It would be replacing one evil with another," said the anti-drugs baron Ivanov. "And why on earth would we do that?" Gennady Onischenko, the country's top doctor, repeatedly dismisses methadone as "still a narcotic".

In a major government anti-drug strategy launched last June, there was no mention of substitution therapy, even though Moscow says it is now focused on reducing the demand for drugs. That means that Russia's measly four federal and 77 regional rehabilitation centers will continue to treat addicts with psychotherapy, counseling or simple painkillers.

**Chained To Bed Frames**

The vacuum created by the lack of effective substitution therapies was highlighted in an incident last October in the Ural Mountains town of Nizhny Tagil. Anti-drugs activist Yegor Bychkov, 23, was sentenced to three and a half years in prison for kidnapping drug addicts. Bychkov said he had received permission from the addicts' parents to forcibly take their sons and chain them to steel bed frames while they underwent a painful detox.

Anti-drugs chief Ivanov praised Bychkov, saying he had acted in good will; the head of the parliamentary health committee Olga Borzova said the state was to blame for his arrest as he had become desperate.

The Russian Orthodox Church also weighed in. Though its official stance is against sex education and it regards heroin use as a sin, it has set up its own rehabilitation centers which offer religious guidance. The Church also holds regular discussions with the UN over the HIV/AIDS crisis.

Unfortunately, those sorts of initiatives may be risky. Almost two years ago, the General Prosecutor's Office was ordered by Russia's Security Council to beef up prosecutorial measures against non-governmental organizations which advocate substitution therapy. Since then, activists distributing free needles have been detained on charges of aiding illegal drug use.

"Russian government officials consistently promote falsehoods about harm reduction, and deter those who speak in favor of them," the IHRA's Rick Lines says. "Speaking honestly about the vast body of evidence supporting the effectiveness of methadone is a dangerous thing to do (in Russia)."

That may be why relations between the UN's Global Fund to Fight AIDS, Tuberculosis and Malaria—which has been pushing for methadone legalization—and Russia's health ministry ruptured at the end of last year. The Global Fund provides the most finance for HIV/AIDS prevention in Russia and granted $351 million to Russia for 2004-11. Now $16 million of that allocation remains, and is at risk of being cut this year.

Worse, say global health experts and local NGOs, is the health ministry's decision to scrap the Global Fund's needle distribution, HIV awareness and medication programs. "They proved ineffective and we shall not continue them after 2011," said Alexander Vlasov, the ministry's spokesman.

In October, the health ministry directly accused the Global Fund of making the HIV epidemic worse. "In the regions where these (Global Fund needle) programs were operating, the spread of HIV infection increased three-fold," minister Tatyana Golikova told a narcology conference.

The Fund says it is keeping up a dialogue with the Health Ministry. But global health experts warn that the decision to end the Global Fund's work in Russia will be catastrophic. "Russia will fall behind and lose the achievements made so far," warned IAS president Katabira. "We will not be able to recover the situation."

(Additional reporting by Ee Lyn Tan in Beijing, Maria Stromova in Moscow and Roman Kozhevnikov in Dushanbe; editing by Simon Robinson and Sara Ledwith)
Up to 30% of People with HIV Develop Neutralizing Antibodies that May Slow Disease Progression

**SUMMARY:** Between 10% and 30% of people with HIV produce broadly cross-reactive antibodies against the virus during the first few years of infection, according to research published in the January 13, 2011, edition of *PLoS Pathogens*. These early antibodies, which target a conserved region of HIV's outer envelope, are associated with lower plasma viral load, and investigators suggested their findings could aid development of an effective vaccine.

Below is the text of a press release describing the study issued by the Public Library of Science, which publishes this and other open-access online journals.

**Researchers Report on the Early Development of Anti-HIV Neutralizing Antibodies**

New findings are bringing scientists closer to an effective HIV vaccine. Researchers from Seattle Biomedical Research Institute (Seattle BioMed), Vanderbilt University and the Ragon Institute of MGH, MIT and Harvard report findings showing new evidence about broadly-reactive neutralizing antibodies, which block HIV infection. Details are published January 13 in the open-access journal *PLoS Pathogens*.

According to author Leo Stamatatos, PhD, director of the Viral Vaccines Program at Seattle BioMed, a major stumbling block in the development of an effective vaccine against HIV is the inability to elicit, by immunization, broadly reactive neutralizing antibodies (NAbs). These antibodies bind to the surface of HIV and prevent it from attaching itself to a cell and infecting it. However, a fraction of people infected with HIV develop broadly neutralizing antibodies (bNAbs) capable of preventing cell-infection by diverse HIV isolates, which are the type of antibodies researchers wish to elicit by vaccination.

"We've found that the people who develop broadly-reactive neutralizing antibodies—which are about 30% of those infected—tend to have a healthier immune system that differs from others who don't develop those antibodies," Stamatatos explained, saying that these antibodies target only a few regions of HIV which is good from the standpoint of vaccine development. "It gives us less to target," he said.

In addition, the new findings show that these antibodies are generated much sooner than previously thought, in some cases as soon as a year after infection.

"These studies provide a strong rationale to begin teasing out the early immunological signals that allow some individuals, but not others, to mount broadly reactive neutralizing antibody responses," adds co-author Galit Alter, PhD.

"Now we know that these broadly-reactive neutralizing antibodies don't develop simply by chance and we can work to understand what makes this 30% of the HIV-infected population different," Stamatatos explained. By understanding that, we can hopefully use that information to design new immunogens and immunization protocols that can mimic the early events that lead to the development of such antibodies during natural infection." 1/25/11

**Reference**

**Other Source**

New Report Outlines Persistent Health Disparities in U.S.

**SUMMARY:** Health disparities based on race/ethnicity and socioeconomic status remain a persistent problem in the U.S. despite efforts to combat them, according to a new report from the Centers for Disease Control and Prevention (CDC) published in the January 14, 2011, *Morbidity and Mortality Weekly Report* supplement. Infant mortality remains higher among African-Americans, poor people spend more days sick than those with higher incomes, and disparities in HIV infection rates are widening, with blacks and gay/bisexual men bearing the greatest burden.

Below is the text of the report’s Foreword by CDC director Thomas Frieden. The full *Health Disparities and Inequalities Report* is available online at [www.cdc.gov/mmwr/preview/ind2011_su.html](http://www.cdc.gov/mmwr/preview/ind2011_su.html).

**Health Disparities and Inequalities Report – Foreword**

*Thomas R. Frieden, MD, MPH*

*Director, CDC*

Since 1946, CDC has monitored and responded to challenges in the nation's health, with particular focus on reducing gaps between the least and most vulnerable U.S. residents in illness, injury, risk behaviors, use of preventive health services, exposure to environmental hazards, and premature death. We continue that commitment to socioeconomic justice and shared responsibility with the release of *CDC Health Disparities and Inequalities in the United States—2011*, the first in a periodic series of reports examining disparities in selected social and health indicators.
Health disparities are differences in health outcomes between groups that reflect social inequalities. Since the 1980s, our nation has made substantial progress in improving residents' health and reducing health disparities, but ongoing racial/ethnic, economic, and other social disparities in health are both unacceptable and correctable. Some key findings of this report include:

- Lower income residents report fewer average healthy days. Residents of states with larger inequalities in reported number of healthy days also report fewer healthy days on average. The correlation between poor health and health inequality at the state level holds at all levels of income.

- Air pollution-related disparities associated with fine particulates and ozone are often determined by geographical location. Local sources of air pollution, often in urban counties, can impact the health of people who live or work near these sources. Both the poor and the wealthy in these counties can experience the negative health effects of air pollution; racial/ethnic minority groups, who are more likely to live in urban counties, continue to experience a disparately larger impact.

- Large disparities in infant mortality rates persist. Infants born to black women are 1.5 to 3 times more likely to die than infants born to women of other races/ethnicities.

- Men of all race/ethnicities are two to three times more likely to die in motor vehicle crashes than are women, and death rates are twice as high among American Indians/Alaska Natives.

- Men of all ages and race/ethnicities are approximately four times more likely to die by suicide than females. Though American Indians/Alaska Natives, who have a particularly high rate of suicide in adolescence and early adulthood, account for only about 1% of the total suicides, they share the highest rates with Non-Hispanic whites who in contrast account for nearly 5 of 6 suicides. The suicide rate among AI/ANs and non-Hispanic whites is more than twice that of blacks, Asian Pacific Islanders and Hispanics.

- Rates of drug-induced deaths increased between 2003 and 2007 among men and women of all race/ethnicities, with the exception of Hispanics, and rates are highest among non-Hispanic whites. Prescription drug abuse now kills more persons than illicit drugs, a reversal of the situation 15-20 years ago.

- Men are much more likely to die from coronary heart disease, and black men and women are much more likely to die of heart disease and stroke than their white counterparts. Coronary heart disease and stroke are not only leading causes of death in the United States, but also account for the largest proportion of inequality in life expectancy between whites and blacks, despite the existence of low-cost, highly effective preventive treatment.

- Rates of preventable hospitalizations increase as incomes decrease. Data from the Agency for Healthcare Research and Quality indicate that eliminating these disparities would prevent approximately 1 million hospitalizations and save $6.7 billion in health-care costs each year. There also are large racial/ethnic disparities in preventable hospitalizations, with blacks experiencing a rate more than double that of whites.

- Racial/ethnic minorities, with the exception of Asians/Pacific Islanders, experience disproportionately higher rates of new human immunodeficiency virus diagnoses than whites, as do men who have sex with men (MSM). Disparities continue to widen as rates increase among black and American Indian/Alaska Native males, as well as MSM, even as rates hold steady or are decreasing in other groups.

- Hypertension is by far most prevalent among non-Hispanic blacks (42% vs 28.8% among whites), while levels of control are lowest for Mexican Americans. Although men and women have roughly equivalent hypertension prevalence, women are significantly more likely to have the condition controlled. Uninsured persons are only about half as likely to have hypertension under control than those with insurance, regardless of type.

- Rates of adolescent pregnancy and childbirth have been falling or holding steady for all racial/ethnic minorities in all age groups. However, disparities persist as birth rates for
Hispanics and non-Hispanic blacks are 3 and 2.5 times those of whites, respectively.

More than half of alcohol consumption by adults in the United States is in the form of binge drinking (consuming four or more alcoholic drinks on one or more occasion for women and five or more for men). Younger people and men are more likely to binge drink and consume more alcohol than older people and women. The prevalence of binge drinking is higher in groups with higher incomes and higher educational levels, although people who binge drink and have lower incomes and less educational attainment levels binge drink more frequently and, when they do binge drink, drink more heavily. American Indian/Native Americans report more binge drinking episodes per month and higher alcohol consumption per episode than other groups.

Tobacco use is the leading cause of preventable illness and death in the United States. Despite overall declines in cigarette smoking, disparities in smoking rates persist among certain racial/ethnic minority groups, particularly among American Indians/Alaska Natives. Smoking rates decline significantly with increasing income and educational attainment.

Differences in health based on race, ethnicity, or economics can be reduced, but will require public awareness and understanding of which groups are most vulnerable, which disparities are most correctable through available interventions, and whether disparities are being resolved over time. These problems must be addressed with intervention strategies related to both health and social programs, and more broadly, access to economic, educational, employment, and housing opportunities. The combined effects of programs universally available to everyone and programs targeted to communities with special needs are essential to reduce disparities. I hope CDC’s partners will use this periodic report to better understand and address disparities and help all persons in the United States live longer, healthier, and more productive lives.

Reference

Gender, Race, and Geographic Disparities in HIV/AIDS Outcomes

SUMMARY: Women, blacks, and people living in the southern U.S. had poorer HIV treatment outcomes than other groups, according to a study of more than 2000 seroconverters described in the February 15, 2011 Journal of Infectious Diseases. People from these disadvantaged populations were less likely to start antiretroviral therapy (ART) and more likely to experience HIV/AIDS-related events over 8 years of follow-up; those who started treatment, however, responded equally well after the first 6 months.

By Liz Highleyman

Research over the past 3 decades looking at the effects of demographic factors such as sex, race/ethnicity, and socioeconomic status on HIV and its treatment has produced conflicting results. Some studies have suggested that women and people of color respond less well to ART, for example, but others have shown that such differences are attributable to poorer access to care.

In the present study, Amie Meditz from the University of Colorado and colleagues sought to determine whether sex and race/ethnicity influence clinical outcomes following primary HIV infection. This analysis followed people who were identified as HIV positive within 1 year after infection, so it was not affected by the issue of early vs late diagnosis—a confounding factor in many studies.

The analysis included 2277 participants in the Acute Infection and Early Disease Research Program, a multi-center observational cohort of individuals (mostly from North America and Australia) diagnosed with acute or recent HIV infection during the ART era. A limitation of the study was that only 5.4% of participants were women. The researchers classified participants as “white” or "non-white," with most of the "non-whites" being black. The majority (77%) of men were white, while the majority of women (55%) were non-white. Participants were followed for up to 8 years (average about 4.5 years).

Results

At the time of enrollment, women had a lower HIV viral load (average .40 log copies/mL less) and higher CD4 T-cell count (66 cells/mm3 more) than men, after controlling for age and race/ethnicity.

Women were less likely than men to report symptoms of early HIV infection, or acute
retroviral syndrome.

- 68.5% of men and 63.7% of women started ART during the study.
- Non-white women and men were significantly less likely to start ART at any time point compared with white men.
- White women, however, were somewhat more likely to start ART than white men.
- People from the southern U.S. were less likely to start treatment compared with those from other regions.
- Sex and race/ethnicity were not associated with significant differences in virological or immunological response to ART after 6 months.
- During follow-up, women were more than twice as likely as men (2.17-fold) to experience at least 1 HIV-related event.
- Non-white women were more likely than any other group to experience HIV or AIDS events, after adjusting for ART use and injection drug use:
  - HIV-related events, non-white women: 64%;
  - HIV-related events, other groups combined 21%;
  - AIDS-defining events, non-white women: 22%;
  - AIDS-defining events, other groups combined: 6%.
- Non-white women were also significantly more likely than other groups to have their CD4 count fall below 200 cells/mm3 during follow-up.
- By 8 years after diagnosis, there were significant differences in proportions of people who experienced at least 1 HIV/AIDS event:
  - 78% of non-white participants in the southern U.S.;
  - 37% of white participants in the southern U.S.;
  - 24% of white participants in other regions;
  - 17% of non-white participants in other regions.
- Mortality was low overall, and did not differ significantly between women and men (0.8% vs 0.7%, respectively).

"Despite more favorable clinical parameters initially, female HIV-1-seroconverters had worse outcomes than did male seroconverters," the study authors concluded. "Elevated morbidity was associated with being non-white and residing in the southern United States."

While women, non-whites, and southerners were less likely to start ART, this did not fully account for differences in outcomes, they elaborated in their discussion, suggesting that these disparities could be attributable in part to socioeconomic factors including "access to health care, health behaviors, lifestyle, and environmental exposures." Given that differences in HIV outcomes between men and women are typically not observed in studies outside the U.S., they added that "sex differences in HIV-related morbidity observed in this study are not biologically based but are the result of socioeconomic conditions specific to the United States."

In an accompanying editorial, Carlos del Rio and Wendy Armstrong from Emory University cautioned that socioeconomic factors play an important role in determining HIV disease outcomes—at both the individual and population levels—and "although theoretically modifiable, they represent complex challenges that are beyond the traditional influence of public health." 1/25/11

References
Operation makes dementia patients faster and smarter
Researchers from the University of Gothenburg and Sahlgrenska University Hospital are the first in the world to show that an operation can help patients with dementia caused by white matter changes and hydrocephalus.

Presented in the American Journal of Neurosurgery, the results are based on the world’s first study to demonstrate the effects of a shunt operation using a placebo control. 14 patients were followed for an average of three and a half years after the operation, with half being given a non-functioning shunt – in other words a sham operation – and the other half a functioning shunt. This is the equivalent to the placebo given in drug trials to determine how much of the treatment’s effect is down to the patient’s and others’ expectations.

"For obvious reasons, this is problematic in a surgical context and surgical placebo studies are highly unusual," says Magnus Tisell, docent at the Sahlgrenska Academy and consultant neurosurgeon at Sahlgrenska University Hospital. "However, if you can actually do this kind of study, the level of evidence is the highest possible – class 1."

The researchers found that patients' mental functions and ability to walk improved tangibly after having a shunt inserted. Half were given an open shunt right from the start and showed immediate improvement, while the other half were initially given a closed shunt and improved only after three months when the shunt was opened.

"Shunt operations have long been used for hydrocephalus, but this study offers more scientifically conclusive results to support the effect of the treatment, and also shows that shunt operations can help far more patients than previously believed with their walking and memory," says Tisell.

Surgery is not generally used today for patients with hydrocephalus and white matter changes. But the researchers’ findings pave the way for a brand new group of patients who could benefit from a shunt operation.

"We believe that far more patients than is currently the case could benefit from a shunt operation, which will require more resources," says Tisell. "We also need to find out more about which patients are good candidates for the operation and which shunt is best in each particular case."

Hydrocephalus
Hydrocephalus is caused by excessive fluid collecting in the brain’s cavities. Patients often have problems walking, and their ability to think and remember is also affected. The fluid can be drained through a shunt, a narrow plastic tube that is surgically inserted into one of the brain’s cavities and linked to the stomach or heart. In some cases keyhole surgery can make it possible for the fluid to be absorbed into the bloodstream. Around 400 adults a year receive surgery for different types of hydrocephalus in Sweden.

Publication data
Journal: Journal of Neurosurgery, Title: Shunt surgery in patients with hydrocephalus and white matter changes.

01.25.11—New Discovery Could Lead to Vaccines for Plague and Bacterial Pneumonias
Saranac Lake, N.Y. – There is an ongoing battle in the “war on terror” that remains mostly unseen to the public—a race between scientists working to develop a vaccine to protect against plague and the terrorists who seek to use plague as a weapon.

“Governments remain concerned that bioweapons of aerosolized Yersinia pestis, the bacteria that causes plague, could kill thousands,” said Stephen Smiley, a leading plague researcher and Trudeau Institute faculty member.

The anthrax scare that followed the terror attacks of September 11, 2001, made the threat of bioterrorism real and led to a surge in federal funding into research aimed at heading off such threats.

According to Dr. Smiley, there is no licensed plague vaccine in the United States. Together with postdoctoral associate Jr-Shiuan Lin, he is working to develop a vaccine that will protect members of the armed services and public from a “plague bomb.”

Yersinia pestis is arguably the most deadly bacteria known to man. Plague infections of the lung, known as pneumonic plague, are extremely lethal. The bacteria, which grow both inside and outside the cells of the lung, usually lead to death within a week of infection.

Most of the plague vaccine candidates that have been studied aim to stimulate B cells to produce plague-fighting antibodies. However, animal studies suggest that antibodies may not be enough to protect humans from pneumonic plague. The Smiley laboratory has shown that T cells can also fight plague. The lab previously demonstrated that a single immunization with an experimental vaccine stimulates the production of T cells that provide partial protection against pneumonic plague.
New data, reported in the current issue of The Journal of Immunology, show that a second immunization, or booster, improves the protection provided by T cells. “It is particularly exciting that the boost seems to improve protection by increasing a newly described type of T cell, which we call a Th1-17 cell,” said Dr. Smiley. These cells have characteristics of both Th1 cells, which defend against intracellular bacteria, and Th17 cells, which specialize at killing extracellular threats.

This research is focused primarily on thwarting the use of plague as a bioweapon. However, small, natural outbreaks of plague continue to this day. A plague vaccine will protect against both naturally occurring outbreaks and those that have been manufactured.

Additionally, Dr. Smiley believes these Th1-17 cells may be important in fighting other kinds of pneumonia: “Bacterial pneumonia is one of the most common causes of death in hospitals and, like plague, many of these pneumonias are caused by bacteria that grow both inside and outside the cells of our bodies.”

Dr. Smiley’s studies are funded by the Trudeau Institute and grants from the National Institutes of Health.

The Trudeau Institute is an independent, not-for-profit, biomedical research organization, whose scientific mission is to make breakthrough discoveries leading to improved human health. Trudeau researchers are identifying the basic mechanisms used by the immune system to combat viruses like influenza, mycobacteria, such as tuberculosis, parasites and cancer, so that better vaccines and therapies can be developed for fighting deadly disease.

**Genetic Sequencing Alone Doesn’t Offer a True Picture of Human Disease, Research Suggests**

ScienceDaily (Jan. 24, 2011) — Despite what you might have heard, genetic sequencing alone is not enough to understand human disease. Researchers at Duke University Medical Center have shown that functional tests are absolutely necessary to understand the biological relevance of the results of sequencing studies as they relate to disease, using a suite of diseases known as the ciliopathies which can cause patients to have many different traits.

"Right now the paradigm is to sequence a number of patients and see what may be there in terms of variants," said Nicholas Katsanis, Ph.D. "The key finding of this study says that this approach is important, but not sufficient. If you really want to be able to penetrate, you must have a robust way to test the functional relevance of mutations you find in patients. For a person at risk of type 2 diabetes, schizophrenia or atherosclerosis, getting their genome sequenced is not enough—you have to functionally interpret the data to get a sense of what might happen to the particular patient."

"This is the message to people doing medical genomics," said lead author Erica Davis, Ph.D., Assistant Professor in the Duke Department of Pediatrics, who works in the Duke Center for Human Disease Modeling. "We have to know the extent to which gene variants in question are detrimental—how do they affect individual cells or organs and what is the result on human development or disease? Every patient has his or her own set of genetic variants, and most of these will not be found at sufficient frequency in the general population so that anyone could make a clear medical statement about their case."

Davis, working in the lab of Katsanis, and in collaboration with many ciliopathy labs worldwide, sequenced a gene, TTC21B, known to be a critical component of the primary cilium, an antenna-like projection critical to cell function.

While a few of the mutations could readily be shown to cause two main human disorders, a kidney disease and an asphyxiating thoracic condition, the significance of the majority of DNA variants could not be determined. Davis then tested these variants in a zebrafish model, in which many genes are similar to humans, and showed that TTC21B appears to contribute disease-related mutations to about 5 percent of human ciliopathy cases.

The study, which appears in *Nature Genetics* online on Jan. 23, shows how genetic variations both can cause ciliopathies and also interact with other disease-causing genes to yield very different sets of patient problems.

Katsanis, the Jean and George Brumley Jr., M.D., Professor of Pediatrics and Cell Biology, and Director of the Duke Center for Human Disease Modeling, is a world expert in ciliopathies such as Bardet-Biedl Syndrome, in which the primary cilium of cells is abnormal and leads to a host of problems. About one child in 1,000 live births will have a ciliopathy, an incidence that is in the range of Down’s syndrome, said Katsanis.
"By sequencing genes to identify genetic variation, followed by functional studies with a good experimental model, we can get a much better idea of the architecture of complex, inherited disorders," Katsanis said. "Each individual with a disease is unique," Davis said. "If you can overlay gene sequencing with functional information, then you will be able to increase the fidelity of your findings and it will become more meaningful for patients and families."

It will take more laboratories doing more pointed studies like this one to get a fuller picture of the ciliopathies and other diseases, Davis said.

Katsanis noted that it will take true collaboration within many scientific disciplines as well as scientific finesse to get at the true roots of complex diseases.

"Brute force alone—sequencing—will not help," he said. "Technology is of finite resolution. You must have synthesis of physiology, cell biology, biochemistry and other fields to get true penetration into medically relevant information."

Numerous scientists from other institutions were involved, including those from Johns Hopkins University, University of Pennsylvania, University of Birmingham in the United Kingdom, Universite Louis Pasteur, St. James University Hospital in Leeds, University of Michigan, Baylor College of Medicine, the National Human Genome Research Institute and others.

Accelerated Evolution Used to Develop Enzymes That Provide Protection Against Nerve Gas ****

ScienceDaily (Jan. 25, 2011) — Protection against nerve gas attack is a significant component of the defense system of many countries around the world. Nerve gases are used by armies and terrorist organizations, and constitute a threat to both the military and civilian populations, but existing drug solutions against them have limited efficiency.

A multidisciplinary team of scientists at the Weizmann Institute of Science succeeded in developing an enzyme that breaks down such organophosphorus nerve agents efficiently before damage to nerves and muscles is caused. Their results have recently been published in the journal *Nature Chemical Biology*. Recent experiments performed in a U.S. military laboratory (USAMRICD) have shown that injecting a relatively small amount of this enzyme into animals provides protection against certain types of nerve agents, for which current treatments show limited efficacy.

Nerve agents disrupt the chemical messages sent between nerve and muscle cells, causing loss of muscle control, and ultimately leading to death by suffocation. Nerve agents interfere with the activity of acetylcholinesterase, the enzyme responsible for the breakdown of the chemical messenger—acetylcholine. As a result, acetylcholine continues to exert its effect, resulting in constant muscle contraction throughout the body.

Several drugs exist that are used to treat cases of nerve agent poisoning. Although these drugs are somewhat effective when exposed to small doses of the nerve agent, they do not provide protection against high-dose exposure; they are not effective against all types of nerve agents; or they cause serious side effects. Neither are they able to prevent nor repair cerebral and motor nerve damage caused by the nerve agent.

An ideal solution to the problem is to use enzymes—proteins that speed up chemical reactions—to capture and break down the nerve agent before it gets the chance to bind to the acetylcholinesterase, thereby preventing damage. The main obstacle facing the realization of this idea, however, is that nerve agents are man-made materials and therefore, evolution has not developed natural enzymes that are able to carry out this task.

Scientists worldwide have previously succeeded in identifying enzymes that are able to break down similar materials, but these enzymes were characterized by low efficiency. Large amounts of the enzyme were therefore required in order to break down the nerve agent, rendering their use impractical.

This is where Prof. Dan Tawfik of the Weizmann Institute’s Biological Chemistry Department enters the picture. Tawfik’s group developed a special method to artificially induce “natural selection” of enzymes in a test tube, enabling them to engineer “tailor-made” enzymes.

The method is based on introducing many mutations to an enzyme, and scanning the variety of mutated versions that were created in order to identify those that exhibit improved efficiency. These improved enzymes then repeatedly undergo further rounds of mutations and selection for higher efficiency. In previous studies, Tawfik showed that this method can improve the efficiency of enzymes by factors of hundreds and even thousands.
For the current task, Tawfik selected an enzyme that has been extensively studied in his laboratory, known as PON1. The main role of this enzyme, found naturally in the human body, is to break down the products of oxidized fats that accumulate on blood vessel walls, thus preventing atherosclerosis. But PON1 seems to be a bit of a "moonlighter" as it has also been found to degrade compounds belonging to the family of nerve agents.

However, because this activity has not fully evolved and developed through natural selection, its efficiency in carrying out the task remains very low. But by using the directed evolution method, scientists hope that they will be able to evolve this random "moonlighting" activity into PON1's main "day job," which would be carried out more quickly and efficiently than before.

In the first phase, Tawfik and his team, including research fellow Dr. Moshe Goldsmith and postdoctoral student Dr. Rinkoo Devi Gupta, induced a number of mutations in PON1—some random and others directed at key sites on the enzyme. To identify the most effective PON1 mutants, the scientists joined forces with Yacov Ashani of the Structural Biology Department.

The method that the scientists developed closely mimics what happens in the body upon exposure to nerve agents: They put the acetylcholinesterase in a test tube together with a specific mutant PON1 enzyme that they wanted to test, and added a small amount of nerve agent to it. In cases where the acetylcholinesterase continued to function properly, it could be concluded that PON1 rapidly degraded the nerve agent before it was able to cause damage to the acetylcholinesterase.

After several rounds of scanning, the scientists succeeded in indentifying active mutant enzymes, which are able to break down the nerve agents soman and cyclosarin effectively before any damage is caused to the acetylcholinesterase. These mutant enzymes have been structurally analyzed by a team of scientists from the Structural Biology Department, which included Profs. Joel Sussman and Israel Silman, and research student Moshe Ben-David. Further experiments have shown that when these enzymes were given as a preventative treatment before exposure, they afforded animals near-complete protection against these two types of nerve agents, even when exposed to relatively high levels.

The scientists plan to further expand the scope and develop preventive treatment that provides protection against all types of existing nerve agents. They are also trying to develop enzymes with high enough efficiency to be able to very rapidly break down the nerve agent so they could be used to prevent the lethal effects of nerve agents by injection immediately after exposure.

Journal Reference:

Global view of blood cell development reveals new and complex circuitry
Researchers take a systematic approach to catalog factors that control blood cell development

A small pool of stem cells replenishes the human body with about 200 billion new blood cells daily. But the elaborate circuitry that determines if a cell will develop into a T cell, red blood cell, or one of the nine or more other blood cell types remains largely unknown. A research team led by scientists from the Broad Institute and Brigham and Women’s Hospital has taken a systematic approach to help decipher this circuitry, compiling a comprehensive catalog of the factors that determine a blood cell's fate. Their work appears in the January 21 issue of Cell.

The researchers found that blood cells are directed by a multitude of transcription factors, proteins that turn on and off genes. While many previous studies have focused on individual transcription factors or types of blood cells, this study examined the expression and regulation of all transcription factors throughout blood development. The findings point to densely, interconnected circuits that control this process, suggesting that the wiring for blood cell fate is far more complex than previously thought.

"One assumption in the field had been that there are a small number of transcription factors that orchestrate this process," said Aviv Regev, a Broad Institute core member and co-senior corresponding author of the study. "Some people have always thought there would be a lot of factors and that it would just take time to find them. It turns out there are more masters than we would have thought."

The researchers looked globally at how the expression of all 20,000 or so genes in the genome change as blood stem cells become specialized cell types (a process known as differentiation). They discovered that while a small fraction of genes are uniquely expressed in a single type of cell, other genes are more broadly expressed — present in a variety of cell types but at varying levels. Some of these genes are turned on in the blood stem cells and switched off at certain points in development while others are reused in
several parallel developmental branches. The researchers found about 80 of these patterns of variable genes, called modules. Each kind of specialized cell has a unique profile, or combination, of these modules.

Looking at the genes modulated in the course of healthy cell development could give researchers clues about what events lead to blood cancers, such as leukemia, a disease where differentiation has gone wrong.

"When you look at leukemia cells beneath a microscope, they have a lack of differentiation and they look abnormal," said Broad associate member Ben Ebert, an associate physician of hematology at Brigham and Women's Hospital and a senior corresponding author of the study. "They've ended up in a place that doesn't exist in normal development." Now that the researchers have a clearer picture of the modules that normal cells exhibit, they can apply this knowledge to help identify the similarities and critical changes in leukemia cells' profiles.

"Leukemia cells have the same set of building blocks as normal blood cells – some, they keep the right way so a piece of the profile is right, and a piece of the profile is wrong," said Regev, who is also an assistant professor in the department of biology at MIT and an Early Career Scientist at Howard Hughes Medical Institute.

"Already, many people are asking for the data. Other groups can now combine their data with ours to ask new questions," said Novershtern. "What's also exciting is that people can see the power of computational models, tools that can be used to find new biological insights from the data."

Rapid ageing of T-cells after HIV infection could help explain cancers, diseases of ageing
Keith Alcorn
Published: 27 January 2011
HIV infection can cause a specific sub-group of CD4 T-cells to age by as much as 20 or 30 years within three years of contracting the virus, American researchers report. This ageing process could help to explain the unusual rate of diseases associated with the elderly in HIV-infected people in their middle years, they speculate.

Cancers, cardiovascular disease and bone thinning (osteoporosis) have been observed either at high rates or at younger ages in people with HIV infection, leading to speculation that HIV infection and the inflammation associated with prolonged activation of the immune system by the virus may be the cause of the early onset of diseases of ageing in HIV-positive people.

Many of the conditions associated with ageing are influenced by the loss of immune function with age. Some researchers have become interested in determining whether HIV has direct effects on the immune system that speed up the ageing process, effectively leaving a person with HIV infection with the immune system of a much older person.

T-cell ageing can be measured by looking at the ends of chromosomes within the cells. The ends of chromosomes are protected by telomeres, which stop them from being damaged or fusing together. As we age, the telomeres become shorter. Eventually the telomeres become so short that the cell ceases to function properly.

The study reported this week in the journal PLoS One, conducted by UCLA AIDS Institute, shows that among people infected with HIV, two subsets of naïve CD4+ T cells show signs of telomere shortening equivalent to 20 to 30 years of ageing within two to three years of infection.

A similar rate of ageing happened in younger (20-39) and older (39-58) adults.

Patients also experienced a decline in the number of naïve CD4+ cells in comparison to age-matched controls, even though this group of CD4+ cells is not the primary target of HIV infection, nor the primary sub-group depleted as a result of HIV infection. Indeed, this subset was more depleted than any other subset of CD4+ cells.

Naïve CD4+ T-cells are needed to respond to new infections. As we age, they become less plentiful, making it more difficult for the immune systems of older people to respond to new infections they haven’t encountered before. These cells are also needed to develop immunity after vaccination, which is why elderly people are less likely to develop protection after vaccination than younger people.

In adults with HIV aged 20-39 the naïve cell subset was 2.9 times smaller than in age-matched HIV-negative controls (p=0.0007). The difference in this subset was not significant in those aged 39 to 58. What’s more, the naïve T cell subset being studied (CD31 CD4+) is not restored to normal levels for a person’s age after they start antiretroviral treatment. Looking at a separate sample of patients from the
The researchers speculate that the increased rate of some cancers seen in people with HIV when compared to age-matched controls, as well as a higher rate of some infections, may be due to the immune defects detected by this study.

The researchers also suggest that accelerated HIV disease progression in the over-50s could be a consequence of the additive effects of HIV infection and of ageing on this CD4+ T-cell subset.

"Our findings have important implications for the health of both young and old HIV–infected adults," said lead investigator Tammy M. Rickabaugh, an assistant research immunologist in the division of hematology and oncology at the David Geffen School of Medicine at UCLA. "They underscore the importance of developing new approaches to boost immune function to complement current treatments, which are exclusively directed against the virus."

Reference

Doctor who contracted HIV settles High Court action
27/01/11, 9:34 am 263 Views No Comments
A DOCTOR WHO contracted HIV while performing his duties as a surgeon has settled his High Court case against the hospital where he had worked, the HSE, and the state.

The doctor told the court how, on being diagnosed with the virus in 1997, he had to immediately give up his duties. “My life stopped that day,” he said at a previous hearing.

He said that the [absence of mandatory screening](https://www.independent.ie/health/absence-of-mandatory-screening-of-hospital-patients-for-hiv-exposed-him-to-a-risk-of-harm-32233456.html) of hospital patients for HIV exposed him to a risk of harm. Screening was considered “uneconomical” and only very high-risk patients were asked if they were HIV positive, he alleged.

During the three months prior to his infection, he estimated that he had attended to 100 patients, during which time he was required to use a variety of sharp implements. Although he wore latex gloves, as surgeons are required to do, he said that these would often be perforated by implements and bone.

According to various reports, the doctor explained that he had become ill with flu-like symptoms prior to his diagnosis in May 1997. He said that his illness had radically altered his plans for the future, explaining that he and his wife had not been at a stage in their lives to have children prior to his infection, and that the option was now closed to them.

He said that he suffered all the physical and psychological consequences of HIV infection – including illness, tiredness, lethargy and depression – and that he lived in constant fear of infecting his wife, the [Irish Independent](https://www.independent.ie) reports.

The diagnosis also ended his dreams for his career; just before he was diagnosed with HIV he was due to secure a position as a consultant surgeon, he said. His wife had been forced to become the main breadwinner, which was unexpected as he had been extremely successful prior to the diagnosis.

Eugene Gleeson SC, for the hospital, said there was absolutely no suggestion by the hospital that the doctor's HIV infection was acquired in any setting other than an occupational one, the [Irish Times](https://www.irishtimes.com) reports.

However, the defendants denied the doctor’s claim that he had been unduly exposed to harm, saying that he was aware that there was a risk of potential contamination as a result of his duties. They pleaded contributory negligence on the doctor’s part for failing to have adequate regard to the risk of a HIV infection while conducting invasive surgical procedures.

By court order the doctor, the hospital, and the settlement amount may not be disclosed.

Rare HIV Transmission Changed Transplant Practice
On Nov. 13, 2007, the media widely published the news that several HIV transmissions had resulted after donated organs were transplanted from a deceased high-risk donor. Though this was the first such transmission in 20 years, it prompted an "exaggerated" response by some US transplant surgeons, a new study suggests.

CDC-defined high-risk organ donors (HRDs) include those who, in the past five years, have engaged in specific risk behaviors: men having sex with men, drug injecting, and sex work.

Between January and April 2008, researchers surveyed 422 working US transplant surgeons about their attitudes and practices following the 2007 transmission event.
Among respondents, 31.6 percent said they had changed their practice, including 41.7 percent who had decreased use of HRDs and 34.5 percent who emphasized the risks during informed consent counseling. Just 16.7 percent increased their use of nucleic acid testing (NAT), and 6 percent adopted a formal policy. Fear of being sued or hospital pressure was associated with more than a two-fold higher odds of changing practice, with medical risks of HIV associated with an 8.29-fold odds of decreasing HRD use.

“The risk of death while waiting for an organ transplant is far higher for many patients than is the risk associated with these organs,” said study leader Dr. Dorry Segev of the Johns Hopkins University School of Medicine.

In 2009, 14,600 people donated organs, and about 6,700 people died waiting for such a donation. More than 72,000 Americans are on a waiting list for organs.

The 2007 transmission case involved donated organs from a man who had sex with men. Standard antibody tests for hepatitis C and HIV came back negative, and his organs were transplanted into four recipients, who later turned up infected with both viruses. NAT, which can detect more recent HIV infections than antibody tests, is now used at the organ procurement center that distributed the organs in the 2007 case.

The study, “Provider Response to a Rare but Highly Publicized Transmission of HIV Through Solid Organ Transplantation,” was published in the Archives of Surgery (2011;146(1):41-45).

**Schools Advocate STD Testing**

*Hartford Courant*, (01.24.2011) Jesse Leavenworth

Health officials are recommending a high school-based STD prevention intervention in the Manchester area that would include free screenings. The board of education was briefed on the program and was hearing a presentation at its Monday meeting in Lincoln Center.

“We have been very concerned about the numbers [of STD cases] in the young population,” said Maryann Cherniak Lexius, Manchester’s health director. The town recorded 250 chlamydia cases in 2009, up from 199 diagnoses in 2005, and Cherniak Lexius said her office is focused on how to stop local STD increases.

Tenth-graders last spring participated in a pilot program presented in collaboration with the state Department of Health’s STD Control Program. The one-period lesson included graphic slides and the message of abstinence “as the only true prevention,” Cherniak Lexius said. Parents can elect not to have their child participate in the session.

Manchester health officials want to continue the pilot program and begin providing confidential, non-invasive testing in Manchester High School as well as other local high schools. Testing in the school nurse’s office would be during specific periods, and walk-in testing would be available with a state health professional. Under state law, parental consent is not needed for the screenings, Cherniak Lexius said.

“As health educators and health promoters, anything we can do to remove barriers for students to access health care is wise,” said Suzanne Valade, Manchester’s coordinator of school health services.

Town health officials would like to offer the program to all local high school students, said Cherniak Lexius.

**Cervical Cancer Fight Still a Priority**


“... We now have the medical know-how and the tools to stamp out [cervical cancer] once and for all. What we need now, as our country honors National Cervical Cancer Awareness Month, is the will among members of the public health community to make it happen.

“... The [human papillomavirus] vaccine is now available and prevents infection from the two types of HPV that are responsible for 70 percent of all cervical cancers. We have an established screening tool, the Pap test, that identifies cell changes that can signal cervical disease or cancer. We also have newer technology, the HPV test, to help identify women who are at higher risk.

“... The HPV vaccine is recommended for routine administration in girls ages 11 and 12, with a ‘catch-up’ provision for those up to age 26. Studies show, though, that less than one in two young adolescent girls has received it.

“... At least half of all cervical cancer deaths are due to a lack of screening. Yet about 25 percent of women in the US have not been screened in the past three years. Women who have been vaccinated still need to be screened to protect against HPV types not targeted by the vaccine.
“Also, while the Pap test has led to a dramatic decrease in cervical cancer in the US, about one-third of cervical cancer deaths are caused by screening errors with the Pap test, a problem the more sensitive HPV DNA testing could address. The HPV test is available, in conjunction with a Pap test, for women ages 30 and older.

“We need to make cervical cancer prevention a top national health priority. ... The elimination of cervical cancer is an eminently achievable goal. To achieve this vision, a new program—Cervical Cancer-Free America—is driving state and local prevention programs, and ensuring that successful strategies are shared among the states.”

The author is director of Cervical Cancer-Free America. For more information, visit www.cervicalcancerfreeamerica.org.

Malaysia Releases GM Mosquitos Into Wild In Hopes Of Slowing Spread Of Dengue
“Malaysia released about 6,000 genetically modified mosquitoes into a forest in the first experiment of its kind in Asia aimed at curbing dengue fever, officials said Wednesday,” the Associated Press reports. "The field test is meant to pave the way for the use of genetically engineered Aedes aegypti male mosquitoes to mate with females and produce no offspring or ones with shorter lives, thus curtailing the mosquito population." The article describes how a similar trial in the Cayman Islands "resulted in a dramatic drop in the mosquito population in a small area studied by researchers," and the debate surrounding the approach (1/26).

Health Officials To Explore Whether Polio Caused Paralysis Among Several Cholera Patients In Haiti
The Associated Press reports that health officials in Haiti are looking into whether paralysis among four patients infected with cholera in northwestern Haiti was caused by polio. "Local health authorities reported suspected cases on Jan. 10. Of four showing paralysis three died and one is hospitalized in the capital," the news service reports. However, the living patient tested negative for the disease, according to Pan American Health Organization (PAHO) spokeswoman Nyka Alexander, leading officials to believe polio is not behind the paralysis (1/26).

Bacteria possible cause of preterm births
The type of bacteria that colonize the placenta during pregnancy could be associated with preterm birth and other developmental problems in newborns according to research published in the current issue of the online journal mBio®.

"The fetal inflammatory response appears to contribute to the onset of preterm labor, fetal injury and complications, underlying lifetime health challenges facing these children," say the researchers from Harvard Medical School, Brigham and Women's Hospital and Children's Hospital of Boston. "Our data suggest that placental colonization by specific groups of organisms can increase or decrease the risk of a systemic inflammatory condition."

Preterm birth occurs in nearly a half million pregnancies in the United States alone. Despite improved care, preterm and especially extremely low-gestational-age newborns continue to be at a considerably higher risk of morbidity, mortality and developmental problems. Much of this risk is attributable to imbalanced inflammatory responses of the fetus and newborn.

The systemic fetal inflammatory response to intrauterine exposures, especially intrauterine infections, is regarded as an important contributor to the onset and often lifelong consequences of preterm labor, fetal injury and early organ damage. Approximately half of all placenta delivered before the second trimester and 41% of those delivered by Caesarean section harbor microorganisms detectable by culture techniques.

In order to better understand what role, these microorganisms could play in the extremely preterm inflammatory response the researchers analyzed protein biomarkers in dry blood spots obtained from 527 newborns delivered by Caesarean section and cultured and identified the bacteria from their respective placentas.

Placentas colonized primarily by microorganisms commonly associated with the condition know as bacterial vaginosis (BV) were found to be associated with elevated levels of proinflammatory protein in newborns. In contrast, colonization by Lactobacillus species of bacteria (often found in decreased concentrations during BV) were associated with lower levels of proinflammatory proteins.
"Our study supports the concept that the placental colonization with vaginal microorganisms can induce a systemic inflammatory response in the fetus and newborn and that the dominating molecular feature of this response can be dependent on the type of bacteria," says Andrew Onderdonk of Harvard Medical School and Brigham and Women's Hospital, one of the authors of the study. "Our data suggest that the targeting of placental colonization by specific drugs or probiotics during early pregnancy may hold promise for preventing not only preterm birth but also the devastating and far-reaching inflammatory consequences in premature newborns."

mBio® is a new open access online journal published by the American Society for Microbiology to make microbiology research broadly accessible. The focus of the journal is on rapid publication of cutting-edge research spanning the entire spectrum of microbiology and related fields. It can be found online at http://mbio.asm.org.

The journal article can be found online at http://mbio.asm.org/content/2/1/e00280-10

How Pathogenic Bacteria Hide Inside Host Cells
ScienceDaily (Jan. 27, 2011) — A new study into Staphylococcus aureus, the bacterium which is responsible for severe chronic infections worldwide, reveals how the bacteria have developed a strategy of hiding within host cells to escape the immune system as well as many antibacterial treatments. The research, published by EMBO Molecular Medicine, demonstrates how 'phenotype switching' enables bacteria to adapt to their environmental conditions, lie dormant inside host cells and become a reservoir for relapsing infections.

Staphylococcus aureus is a major human pathogen which can be carried by up to 70% of healthy people, and can lead to conditions such as deep tissue infections, osteomyelitis, and chronic lung infections, which are often hard to treat with antibiotics. A key characteristic of these infections is that relapses can occur months or years after an apparent cure.

These relapses, Dr. Bettina Löffler and her team from the Institut für Medizinische Mikrobiologie in Münster, Germany, believe are due to phenotype switching, a change in the bacterial behaviour. After infection and invasion of the patient's host cells, the bacteria form small colony variants (SCVs), tiny bacterial subpopulations that can evade the immune system as well as many antibiotics and grow slowly.

"For the microbiologist, it is difficult to detect SCVs in clinical specimens as they grow slowly, often needing several days to form and so can be easily overlooked in diagnosis," said Löffler. "Our study asked two questions: Is the development of SCVs an integral part of the infection process and what are the dynamics of SCV formation?"

The team performed long-term infection studies with Staphylococcus aureus in cell culture systems and also analysed tissue samples from subacute and chronic human infections.

The research revealed that in all infection models, the bacteria were able to persist within the host for several weeks after the infection, leading to the formation of SCV colonies. This showed that SCVs began to appear following infection, after the immune system response was overcome and that this persistence led to a larger phenotypic diversity of bacteria.

"These studies demonstrate that S. aureus are extreme versatile microorganisms that continuously sense their environmental conditions and can rapidly alter to reflect them," said Löffler. "The formation of SCV colonies is a bacterial phenotype switching strategy which is an integral part of the infection process."

This process enables the bacteria to hide inside host cells without provoking an inflammatory response from the host's immune system. In addition, they might be efficiently protected from antibiotic treatment.

"This strategy means that SCVs can be considered as ‘dormant forms’ of infections which can rapidly regain their full virulence and cause a patient to relapse," concluded Löfler. "This has important clinical implications as it means that targeting phenotype switching could prevent the bacteria from hiding, making the infection more vulnerable to host response and treatment."

Journal Reference:
Food-Borne Bacteria Causes Potentially Fatal Heart Infection

ScienceDaily (Jan. 26, 2011) — Researchers at the University of Illinois at Chicago College of Medicine have found that particular strains of a food-borne bacteria are able to invade the heart, leading to serious and difficult-to-treat heart infections.

The study is available online in the Journal of Medical Microbiology.

The bacteria Listeria monocytogenes is commonly found in soft cheeses and chilled ready-to-eat products. For healthy individuals, listeria infections are usually mild, but for susceptible individuals and the elderly, infection can result in serious illness, usually associated with the central nervous system, the placenta and the developing fetus.

About 10 percent of serious listeria infections involve a cardiac infection, according to Nancy Freitag, associate professor of microbiology and immunology and principle investigator on the study. These infections are difficult to treat, with more than one-third proving fatal, but have not been widely studied and are poorly understood.

Freitag and her colleagues obtained a strain of listeria that had been isolated from a patient with endocarditis, or infection of the heart.

"This looked to be an unusual strain, and the infection itself was unusual," she said. Usually with endocarditis there is bacterial growth on heart valves, but in this case the infection had invaded the cardiac muscle.

The researchers were interested in determining whether patient predisposition led to heart infection or whether something different about the strain caused it to target the heart.

They found that when they infected mice with either the cardiac isolate or a lab strain, they found 10 times as much bacteria in the hearts of mice infected with the cardiac strain. In the spleen and liver, organs that are commonly targeted by listeria, the levels of bacteria were equal in both groups of mice.

Further, the researchers found that while the lab-strain-infected group often had no heart infection at all, 90 percent of the mice infected with the cardiac strain had heart infections. The researchers obtained more strains of listeria, for a total of 10, and did the same experiment. They found that only one other strain also seemed to also target the heart.

"They infected the heart of more animals and were always infecting heart muscle and always in greater number," Freitag said. "Some strains seem to have this enhanced ability to target the heart for infection."

Freitag's team used molecular genetics and cardiac cell cultures to explore what was different about these two strains.

"These strains seem to have a better ability to invade cardiac cells," she said. The results suggest that these cardiac-associated strains display modified proteins on their surface that enable the bacteria to more easily enter cardiac cells, targeting the heart and leading to bacterial infection.

"Listeria is actually pretty common in foods," said Freitag. "And because it can grow at refrigerated temperatures, as foods are being produced with a longer and longer shelf life, listeria infection may become more common. In combination with an aging population that is more susceptible to serious infection, it's important that we learn all we can about these deadly infections."

Journal Reference:
F. Alonzo, L. D. Bobo, D. J. Skiest, N. E. Freitag. Evidence for subpopulations of Listeria monocytogenes with enhanced invasion of cardiac cells. Journal of Medical Microbiology, 2011; DOI: 10.1099/jmm.0.027185-0
Scientists ignore grant to research blood donations by gay men
By Rebecca Lindell, Postmedia News January 27, 2011
Two years after Canadian Blood Services created a $500,000 grant to research if and when gay men can safely donate blood, not a single scientist has applied to do the work.

And officials are baffled by the reluctance.

Current rules bar men who have been sexually active with another man since 1977 from donating blood for his entire lifetime because of fears it would be tainted by HIV. The policy has been hotly contested.

The blood ban against gay men made headlines last year when a lawsuit required an Ontario judge to rule if the rules were discriminatory under the Charter of Rights and Freedoms. She ruled the ban was lawful.

"Researchers of Canada: pay attention. Get on this," said Lorna Tessier, director of public relations for Canadian Blood Services. "It's a fully funded grant opportunity in a very interesting area of research."

Not a single research team has applied for the grant, which is jointly funded by the Canadian Institute for Health Research. Tessier said she doesn't know why.

The research could ultimately open the door for gay men to be added to the donor list.

The existing policy is "unsustainable," said Tessier. However, she said the agency needs researchers to help determine the conditions under which it would be safe to allow gay men to donate blood, research that could then be presented to Health Canada — if it's ever finished.

Canadian AIDS researchers have already argued the ban is outdated and should be eliminated. In an article published in the Canadian Medical Association Journal in May 2010, the researchers argue the ban limits the supply of blood and that it is hypocritical because there are hardly any restrictions on heterosexual donors, regardless of their level of sexual promiscuity.

Dr. Norbert Gilmore, the associate director of the McGill AIDS Centre and one of the authors of the study, said research into the blood ban would go a long way into providing a foundation for change.

"There are a lot of innovative ways to approach this," he said, citing the example of having mock donor clinics for the gay community to see who donates and test their blood or having a rolling study of gay men donating blood.

Door Opens for Gay Blood Donors

Toronto Star, (01.25.2011)
Canadian Blood Services, the nation’s federal blood donor agency, believes a lifetime ban on gay men giving blood is obsolete and wants the government to relax the rules. According to Lorna Tessier, CBS’ director of public relations, “A lifetime ban extending by one year every year is just not sustainable. There have been lots of changes in the environment … in testing [and] … on the international front.”

The policy, which dates from the early days of the AIDS epidemic, bars blood donations by any man who has had sex with another man even once since 1977. The ban pits those arguing safety first against those who believe the practice is discriminatory because certain sexual behaviors, not orientation, pose the real risk.

The debate could be nearing an end as CBS researches the issue and prepares to ask its regulator, Health Canada, to consider shortening the amount of time a gay man must be celibate before donating blood. Tessier said the agency is committed to determining what an appropriate restriction would be and is funding a $500,000 (US $500,379) grant administered by the Canadian Institutes for Health Research.

CBS will formally ask Health Canada to change the policy based on its research findings. However, Health Canada spokesperson David Thomas said in an e-mailed statement that the regulator will not approve any changes that increase risk.

“HIV is not really the issue,” said Canadian Hemophilia Society Executive Director David Page. He said emerging sexually transmitted pathogens with unknown incubation periods have been known to circulate first in the gay community. “It’s tragic for that group of people, but that’s the reality.”

In September, the Ontario Superior Court of Justice ruled that donating blood is not a constitutional right. Justice Catharine Aitken, however, said there is insufficient evidence to support an indefinite deferral period that grows longer every year.
Doctors Get Guidelines for Medicine to Block HIV
San Francisco Chronicle, (01.28.2011) Erin Allday
CDC on Thursday published interim guidelines for providers facing questions about the use of the HIV drugs tenofovir and emtricitabine (TDF/FTC) to prevent sexually acquired HIV infection. In an international trial, TDF/FTC taken orally each day with an adherence rate of at least 90 percent was associated with a 73 percent reduction in risk of HIV infection among men who have sex with men. The MSM in both the treatment and control groups received preventive services, including counseling, condoms, and STD treatment if needed.

While CDC and other US Public Health Service agencies are developing guidelines on the use of TDF/FTC pre-exposure prophylaxis (PrEP), concerns exist about unsafe and potentially less effective PrEP practices that could develop during the interim, CDC said. The agency specifically cited intermittent dosing just before or after sex as a concern. In the trial, MSM who adhered to daily TDF/FTC at less than 90 percent had only a 21 percent reduction in HIV risk, a sharp decline in efficacy.

"PrEP has the potential to contribute to effective and safe HIV prevention for MSM if (1) it is targeted to MSM at high risk for HIV acquisition; (2) it is delivered as part of a comprehensive set of prevention services, including risk-reduction and PrEP medication adherence counseling, ready access to condoms, and diagnosis and treatment of [STDs]; and (3) it is accompanied by monitoring of HIV status, side effects, adherence and risk behaviors at regular intervals," CDC said.

MSM at high risk include those who are not taking other effective risk-reduction measures, such as using condoms; those who have frequent partner changes or concurrent partners in high HIV prevalence settings; and MSM whose sex partners are HIV-positive or of unknown serostatus.

In the San Francisco Bay Area, public health officials could begin a PrEP pilot this summer for men who meet CDC guidelines. The trial would determine how best to deliver PrEP and ensure adherence and condom use.

MSM inquiring about PrEP should first be tested for HIV and other STDs at the outset, CDC noted.

For the full set of interim guidelines, visit: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6003a1.htm?s_cid=mm6003a1_w.

Research Reveals Complete Structure of HIV’s Capsid Shell

SUMMARY: Researchers have uncovered the complete amino acid structure of the cone-shaped internal capsid that contains HIV’s genetic material, according to a report published in the January 20, 2011 issue of Nature. Better understanding of this viral component may aid development of novel targeted anti-HIV therapies.

By Liz Highleyman
Below is the text of a press release issued by the Scripps Research Institute describing the research and its findings.

Scripps Research and University of Virginia Scientists Reveal Complete Structure of HIV's Outer Shell

- The research provides clues for new therapies by shedding light on how the outer coating of the virus forms

La Jolla, CA—January 19, 2011—A team of scientists at The Scripps Research Institute and the University of Virginia has determined the structure of the protein package that delivers the genetic material of the human immunodeficiency virus (HIV) to human cells.

The work is the culmination of studies carried out over the last decade looking at different portions of the cone-shaped container, or the capsid. The final piece of the puzzle, described in an article published in Nature on January 20, 2011, details the structure of the two ends of the cone.

"This paper is a milestone for research from our group," says the study's senior author Mark Yeager, MD, PhD, a Scripps Research professor and staff cardiologist and chair of the Molecular Physiology and Biological Physics Department at The University of Virginia School of Medicine.

A detailed description of the complete HIV capsid will provide a roadmap for developing drugs that can disrupt its formation and thus prevent infection by HIV.

Assembling the Package

HIV binds to receptors on human cells and then delivers the capsid inside them. Once inside a cell, the capsid comes apart, releasing its precious cargo—the virus's genetic material.

HIV then sabotages the cell machinery to make many copies of its genes and proteins. As new viruses are made, the genetic material is packaged into spherical immature capsids that HIV uses to escape from the infected cell. But before these newly released viruses can infect other cells, the immature capsid undergoes a dramatic rearrangement to form the mature, cone-shaped shell.

If formation of the mature capsid is disrupted, the virus is no longer infectious. Thus, new drugs targeting capsid formation could provide valuable additions to the arsenal of existing drugs against HIV.

A "Floppy" Bridge

To develop drugs that disrupt capsid formation, however, scientists first need to know precisely how it is formed.

One technology researchers use to obtain detailed structures of biological molecules is X-ray crystallography. This technique requires growing crystals of a molecule and then bombarding the crystals with X-rays to determine the positions of all the atoms.

But unlike the cone-shaped capsids of other viruses, such as the poliovirus, which have a rigid, symmetrical structure that obediently assembles into crystals, the HIV capsid is flexible and can adopt slightly different shapes.

Part of the reason for this flexibility is the protein that makes up the HIV capsid, the CA protein, consists of two ends held together by a "floppy" bridge.

The main conical capsid contains about 250 of the six-fold units or hexamers. Each end of the cone is then closed off by either five or seven smaller five-fold units or pentamers.

"It is impossible to grow crystals of the entire HIV capsid," says Yeager. As a result, his team used a "divide and conquer approach."

Divide and Conquer

Working primarily with husband-and-wife team Owen Pornillos and Barbie Gan-sers-Pornillos, investigators in his lab, Yeager partitioned the HIV capsid into smaller components, then determined their respective structures.

In a journey that started more than 10 years ago, Yeager's group as well as others generated two-dimensional arrays of the hexagonal CA protein that mimicked the hexagonal lattice of the capsid. A breakthrough came in 2007, when the Yeager group used electron microscopy to visualize the CA lattice at higher resolution, which suggested how the domains of CA are packed together: each CA protein joins hands with the adjacent CA protein molecules to form the hexamer.

Guided by the atomic model based on the EM structure, in 2009 the team engineered the CA hexamers so that they formed three-dimensional crystals suitable for X-ray crystallography. The
researchers were then able to determine the particles’ structures at 2-Angstrom resolution (one Angstrom equals one ten-billionth of a meter).

Having cracked the atomic structure of the hexamer, the investigators turned their attention to the more elusive pentamers.

**Next Came the Pentamer**

In this latest study, Yeager, Pornillos, and Ganser-Pornillos used techniques similar to those they had applied to the hexamers to obtain the crystal structures of the CA pentamers.

The **new structure reveals that five CA proteins link hands at one end, called the N-terminal domain (NTD), to form a circle.** The opposite ends of the CA proteins, called C-terminal domain (CTD), form a floppy belt around this central core. Then, CTD links to CTD to connect adjacent pentamers.

The structure reveals flexibility and mobility both between the central core and belt within each pentamer and at the CTD-CTD interfaces of adjacent pentamers. The **CTD subunits can rotate relative NTDs**. "As a result, each ring can adopt slightly different angles relative to its adjacent rings," says Pornillos, first author of the paper.

The structure of the pentamers is remarkably similar to that of the hexamers, notes Pornillos, with one important difference. **Because pentamers are smaller than hexamers, the amino acids, the building blocks of proteins, at the center of the pentamer ring are closer together than in the hexamer.**

Many amino acids have positive or negative charges. When two amino acids with the same charge are close together they tend to push each other away. One **amino acid in the CA protein, called arginine, with a positive charge, sits smack in the middle of both the hexamer and pentamer ring.**

Because the arginines in the pentamer are packed much closer together, they repel one another, making the pentamer a less stable structure than the hexamer. This may explain why there are many more hexamers in the mature HIV capsid compared to pentamers.

The only place where pentamers are likely to form is at the capsids’ ends, where the linked CA proteins have to bend dramatically to close off the capsid—a feat the pentamer is more apt to perform.

"Arginine is the critical switch between hexamer and pentamer formation," says Yeager. "We can finally explain why the CA protein would make one or the other."

**An Atomic Model of the HIV Capsid**

Having solved the atomic structures of both CA hexamers and pentamers, Yeager and colleagues for the first time were able to build a complete atomic model of the mature HIV capsid.

The researchers now plan to further refine the model using sophisticated computer programs to determine the stability of the structure in different regions and to identify possible "weak" points they can target using newly designed drugs.

They will also begin studying the structure of the immature capsid to determine how this version of the capsid transitions to the mature form—a step in the virus lifecycle that has remained mysterious.

"We don’t have the full story yet, but we have volume one," says Yeager.

Research for paper "Atomic Level Modeling of the HIV Capsid" was funded by the U.S. National Institutes of Health and the Center for the Structural Biology of Host Elements in Egress, Trafficking, and Assembly of HIV (CHEETAH), which is based at the University of Utah and directed by Dr. Wesley Sundquist. 1/28/11

**Reference**


**Expanded HIV Screening and Treatment Could Prevent More than 200,000 New Infections**

**SUMMARY:** One-time HIV screening of the entire adult population plus annual screening of people at higher risk could prevent nearly 7% of projected new infections, while treating more eligible people with antiretroviral therapy (ART) could raise the proportion of averted infections to about 17%, according to research described in the December 21, 2010, *Annals of Internal Medicine*. Investigators estimated that the cost of the combined strategy would be about $21,500 per year of life saved.

**By Liz Highleyman**

It is well known that HIV treatment lowers viral load and consequently decreases the likelihood of passing on the virus through sex or needle sharing. HIV screening enables people to start ART in a timely manner,
and studies also show that when people learn their status, they typically reduce risky behavior that could transmit the virus to other.

Public health experts have called for expanding HIV screening and treatment—perhaps even for all HIV positive people regardless of CD4 T-cell count—as part of a comprehensive approach to prevention.

Adding to the body of mathematical models estimating the effects of "test-and-treat," Elisa Long from Yale School of Management and colleagues looked at how expanded screening, wider use of ART, and interventions to reduce risk behavior might affect the U.S. epidemic.

The researchers constructed a dynamic mathematical model of HIV transmission and disease progression, as well as a cost-effectiveness analysis, using data from published medical literature.

They focused on 2 target populations, one high-risk (injection drug users and men who have sex with men [MSM]), the other low-risk (everyone age 15 to 64 years), over 2 time horizons, 20 years or lifetime. They estimated costs and benefits based on quality-adjusted life-years (QALYs), a measure of survival that takes into account quality of life.

**Results**

- According to the model, 1-time HIV screening of low-risk people plus annual screening of high-risk individuals could prevent 6.7%—or more than 80,000—of a projected 1.23 million new infections over 20 years, if people reduced sexual activity by 20% after testing.
- The cost of this strategy was estimated at $22,382 per quality-adjusted life-year gained.
- Expanding ART use to 75% of eligible individuals could prevent 10.3% of projected new infections, at a cost of $20,300 per quality-adjusted life-year gained.
- A combined screening and expanded treatment strategy could prevent 17.3%—or more than 200,000—of projected infections at a cost of $21,580 per quality-adjusted life-year gained.
- However, if sexual activity did not decrease after testing, expanded screening could prevent just 3.7% of projected new infections.
- Earlier ART initiation at a CD4 count above 350 cells/mm³ could prevent 20% to 28% of new infections.
- Counseling and additional efforts to reduce high-risk behavior could reduce new infections by 65%.
- Annual HIV screening, plus risk-reduction efforts that decrease risky behavior by 50%, plus ART initiation for 90% of symptomatic individuals could reduce new infections to fewer than 35,000 per year, down from the current estimate of approximately 56,000.

Based on these findings, the study authors concluded, "Expanding HIV screening and treatment simultaneously offers the greatest health benefit and is cost-effective."

Importantly, this model did not look at the more controversial approach of treating everyone diagnosed as HIV positive, but rather treating symptomatic people and those with a CD4 count below 350 cells/mm³, the threshold in the previous U.S. ART guidelines—now raised to 500 cells/mm³.

However, the researchers added, "even substantial expansion of HIV screening and treatment programs is not sufficient to markedly reduce the U.S. HIV epidemic without substantial reductions in risk behavior."

"[O]ur analysis highlights the importance of emphasizing risk behavior reduction as HIV screening and treatment becomes increasingly available," they elaborated in their discussion. "For example, in addition to expanded screening and treatment, a 50% reduction in sexual risk behaviors among MSM and needle sharing among injection drug users could prevent 65% of new infections, reducing HIV incidence to approximately 20,000 cases per year. This suggests that programs to reduce risk behavior among high-risk persons will probably be a key component of a successful prevention program. If, however, uninfected persons increase risk behavior after screening, some of the benefits would be attenuated."

Finally, they noted, "Compared with other disease screening programs in the U.S., 1-time HIV screening of low-risk persons and annual screening of high-risk persons is economically attractive, with a cost-effectiveness ratio less than $23,000 per QALY gained. This compares favorably with other accepted interventions, including screening for type 2 diabetes and breast cancer mammography." 1/28/11

**Reference**

Tesamorelin (Egrifta) Now Available to Manage HIV-related Lipodystrophy

SUMMARY: Tesamorelin, the recently approved treatment for lipodystrophy, is now commercially available under the brand name Egrifta, according to a recent announcement from EMD Serono. The company will offer a patient assistance program for low-income individuals and a co-pay assistance program for people with insurance, as well as patient training on how to inject the new medication.

The U.S. Food and Drug Administration (FDA) approved tesamorelin this past November for treatment of lipodystrophy characterized by excess body fat accumulation in HIV positive people taking antiretroviral therapy.

Tesamorelin (formerly known as TH9507) is a synthetic growth hormone-releasing factor that stimulates the pituitary gland in the brain to secrete growth hormone; this indirect approach appears to maintain more stable, natural levels. Clinical trials have shown that tesamorelin significantly reduces abdominal fat with fewer side effects than human growth hormone itself, though fat returns after the drug is discontinued.

Below is the text of EMD Serono’s recent community announcement about the availability of tesamorelin and patient assistance provided by the company. Full prescribing information is now available online at http://www.egrifta.com.

Egrifta Patient Support Information

January 21, 2011—EMD Serono, Inc. is proud to announce the full commercial availability of Egrifta (tesamorelin for injection). We are pleased to provide the full Prescribing Information for Egrifta including Patient Information and Patient Instructions for Use. The Prescribing Information has key information about Egrifta, including its full indication and limitations, clinical data and safety information.

EMD Serono is committed to ensuring that appropriate patients have access to Egrifta. To make this commitment a reality, the following programs and services are now available to support patients in gaining access to and staying on Egrifta.

The AXIS Center

The AXIS Center offers dedicated reimbursement, teaching and adherence support for patients on Egrifta. With a team of dedicated Reimbursement Case Managers, the AXIS Center assists patients throughout the process of getting access to and staying on Egrifta.

The AXIS Center offers in-home or in-office injection training to every new patient through a national network of Injection Trainers. Every new patient also receives an Education Kit that provides video and print administration guides along with other useful tools. Support continues throughout treatment with product support specialists available 24 hours-a-day/7 days-a-week to answer patients’ questions about mixing and injecting Egrifta.

To start the process, licensed healthcare providers must fax a Statement of Medical Necessity (SMN) (i.e., prescription), signed by the healthcare provider, and Patient Authorization, signed by the patient, to the AXIS Center at 866-823-9554. SMNs will be provided by the EMD Serono sales team or can be requested by calling the AXIS Center at 877-714-AXIS (2947).

Co-pay Assistance Program

For commercially insured patients with a prescription drug benefit that covers Egrifta, the Co-pay Assistance Program covers up to $2,400 of patients’ out of pocket cost over a 12-month period. Patients must use the card for the first time in 2011 and can offset up to $200 of their co-pay or coinsurance for up to 12 uses prior to 12/31/12, not more than once every 21 days. Patients may not use the Co-pay Assistance Program if they receive drug benefits from state or federal health care initiatives (including Medicare or Medicaid). This program is not valid in the Commonwealth of Massachusetts.

Patient Assistance Program (PAP)

The PAP program provides free Egrifta for eligible patients who are uninsured or under-insured. Patients must meet other eligibility requirements, including a household income that does not exceed 600% of the Federal Poverty Level (FPL). Patients must also have a diagnosis of the indicated condition and be a resident of the United States. The Egrifta PAP program provides free drug for one year and patients will need to reapply if they seek to continue receiving Egrifta. The Egrifta PAP program is coordinated by the AXIS Center at 877-714-AXIS (2947).

We are excited to be launching Egrifta with a comprehensive set of patient support programs. Our aim is to offer the most relevant programs for patients, so, as always, please provide us with any feedback that you may have. 1/28/11
Origins of the Pandemic: Lessons of H1N1
ScienceDaily (Jan. 12, 2011) — As H1N1 'Swine Flu' returns to the national headlines a new research paper reveals the key lessons about the origins of the 2009 pandemic. The paper, published January 12 in BioEssays, reveals how the pandemic challenges the traditional understanding of 'antigenic shift', given that the virus emerged from an existing influenza subtype.

"H1N1 emerged in February 2009 in Mexico and swept around the globe within 6 months." said Professor Hans Dieter Klenk from Philipps-Universität Marburg. "The conventional ideal is that pandemics are fuelled by new strands which emerge in the human population, yet it was because H1N1 did not conform to this ideal that its spread was so unexpected."

Professor Klenk's review of the pandemic focuses on antigens, substances which trigger the immune system when introduced into the body. Influenza viruses have two antigens, hemagglutinin (HA) and neuraminidase (NA).

"It was widely believed that a pandemic occurs when a virus with a new HA, or a new HA and a new NA that are not recognised by the human immune system emerges and spreads throughout the population," said Klenk, "this is known as antigenic shift."

While it was believed that this process has always involved the introduction of a new NA or HA subtype, the 2009 pandemic revealed that a pandemic can result from a shift within the lineages of the existing subtypes.

"There are 16 HA and 9 NA subtypes, which differ significantly, but contain multiple lineages that were always believed to be too similar to allow antigenic shift. However, this is exactly what occurred in 2009," said Klenk.

In the 2009 outbreak a strain of H1N1 containing new HA and NA lineages caused a pandemic even though H1N1 had already circulated through the human population, thus revealing an antigenic shift from within the same subtype.

"From studying the influenza outbreaks of 1918, 1957 or 1977 it looks as if pandemics only occur when a new HA or NA subtype enters the population. This meant that vaccination against the previous viruses offered little protection against infection by the new strain," concluded Klenk. "However, the 2009 outbreak overturns this rule, revealing that a pandemic may not depend on the introduction of a virus with a new HA subtype. This means future research should not simply monitor one or a few viruses and that plans to deal with pandemics must be flexible enough to handle the unexpected.

Orangutan DNA More Diverse Than Human's, Remarkably Stable Through the Ages
ScienceDaily (Jan. 26, 2011) — Among great apes, orangutans are humans' most distant cousins. These tree dwellers sport a coat of fine reddish hair and have long been endangered in their native habitats in the rainforests of Sumatra and Borneo in Southeast Asia.

Now, an international team of scientists, led by Washington University School of Medicine in St. Louis, has decoded, or sequenced, the DNA of a Sumatran orangutan. With this genome as a reference, the scientists then sequenced the genomes of five additional Sumatran and five Bornean orangutans.

Their research, published Jan. 27 in Nature, reveals intriguing clues about the evolution of great apes, including humans, and showcases the immense genetic diversity across and within Sumatran and Bornean orangutans. Diversity is important because it enhances the ability of populations to stay healthy and adapt to changes in the environment.

"The average orangutan is more diverse—genetically speaking—than the average human," says lead author Devin Locke, PhD, an evolutionary geneticist at Washington University's Genome Center. "We found deep diversity in both Bornean and Sumatran orangutans, but it's unclear whether this level of diversity can be maintained in light of continued widespread deforestation."

The scientists catalogued some 13 million DNA variations in the orangutans. This valuable resource can help conservationists assess the genetic diversity of orangutan populations both in the wild and in captivity and help set priorities for aiding subpopulations based on their genetic health.

The orangutan genome adds detail to the evolutionary tree and gives scientists insights into the unique aspects of human DNA that set man apart from the great apes, their closest relatives. Overall, the researchers found that the human and orangutan genomes are 97 percent identical.
However, in a surprising discovery, the researchers found that at least in some ways, the orangutan genome evolved more slowly than the genomes of humans and chimpanzees, which are about 99 percent similar.

"In terms of evolution, the orangutan genome is quite special among great apes in that it has been extraordinarily stable over the past 15 million years," says senior author Richard K. Wilson, PhD, director of Washington University’s Genome Center, which led the project. "This compares with chimpanzees and humans, both of which have experienced large-scale structural rearrangements of their genome that may have accelerated their evolution."

A genome reads much like an instruction book for creating and sustaining a particular species. The chromosomes are the chapters and within every chapter are paragraphs, sentences, words and single letters, which are like the individual bases of the DNA sequence.

"If you are editing a book on your computer, you can highlight a paragraph and copy and paste it, delete it or invert it," Wilson explains. "Duplications, deletions and inversions of DNA are types of structural variations. When we look at the genomes of humans and chimps, we see an acceleration of structural changes over the course of evolutionary history. But for whatever reason, orangutans did not participate in that acceleration, and that was a surprise."

One possible clue to the lack of structural rearrangement in orangutan DNA is a profound lack of repetitive "Alu" elements. These short stretches of DNA make up about 10 percent of the human genome and can pop up in unexpected places to create new mutations or genetic rearrangements.

The human genome possesses about 5,000 human-specific Alus, while the chimp has about 2,000 chimp-specific Alus.

"In the orangutan genome, we found only 250 new Alu copies over a 15 million-year time span," Locke says. "This is the closest thing we have to a smoking gun that may explain the structural stability in the orangutan genome."

The initial Sumatran orangutan genome was sequenced using legacy technology and cost $20 million to complete. Using more sophisticated technology, the cost of sequencing the additional orangutans dropped substantially to about $20,000 each. The project was funded by the National Human Genome Research Institute, the National Science Foundation and other organizations.

The new research shows that the Sumatran and Bornean orangutans diverged some 400,000 years ago. Earlier estimates had put the split at about 1 million years ago. Today, only about 50,000 Bornean and 7,000 Sumatran orangutans still live in the wild.

But in a finding that seems counterintuitive, the researchers found the smaller population of Sumatran orangutans is genetically more diverse than their Bornean cousins.

"It’s quite a mystery how Sumatran orangutans obtained this genetic diversity or whether there has been cleansing of diversity in the Borneans," Locke explains. "We can begin to search for answers using the catalog of genetic variation we developed."

Studies of orangutans are important because these great apes, in particular, are under intense ecological pressure. Their numbers continue to erode as humans encroach further on their habitat.

"Orangutans spend more than 95 percent of their time in the trees," Locke says. "They travel through the trees, nest in trees and forage for food in trees. But all the genetic diversity in the world can’t save them in the wild if their habitat is destroyed."

Journal Reference:
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Study finds little decline in hepatitis C infections among injection drug users
Research suggests improvements in prevention and treatment efforts needed

[EMBARGOED FOR JAN. 31, 2011] A recent 20-year study of injection drug users (IDUs) in Baltimore found a significant decline in new cases of HIV infection but only a slight decline in new cases of hepatitis C virus (HCV) infection. The findings suggest that efforts to curb blood-borne transmission of these viral infections have had success but must be expanded against the highly transmissible HCV. Researchers from Johns Hopkins School of Public Health and other centers, led by Shruti H. Mehta, PhD, MPH, report the findings in the March 1 issue of The Journal of Infectious Diseases, now available online. (Please see below for a link to the embargoed study online.)

Previous data had suggested that HIV incidence among IDUs has declined. This trend is often attributed in part to harm reduction measures, including needle exchange programs and substance abuse treatment. However, these measures have not been as successful in lowering the rates of HCV incidence and prevalence. For example, HCV infection is nearly 10 times more transmissible by sharing needles than is HIV infection. Sharing a needle even once can be enough to transmit HCV.

The investigators found that new cases of HIV infection declined dramatically across four different time periods during the past 20 years, from 5.5 per 100 person-years (PY) in 1988-’89, to two per 100 PY in 1994-’95, and to zero cases in 1998 and 2005-’08. While researchers also observed reductions in new cases of HCV infection, these were not nearly as substantial: from 22 per 100 PY in 1988-’89, to 17.2 per 100 PY in 1994-’95, to 17.9 in 1998, and to 7.8 per 100 PY in 2005-’08. Overall, cases appeared to decline only among younger IDUs, who had started injecting drugs recently.

According to researchers, these data suggest that "current prevention efforts delay but do not prevent HCV at the population level and will need to be further intensified to reduce risk of HCV infection to the level of HIV." Efforts on both the prevention and the treatment fronts to reduce the reservoir of HCV-infected IDUs will have to be expanded, the investigators concluded.

In an accompanying editorial, Jason Grebeley, PhD, and Gregory J. Dore, MB BS, MPH, PhD, of the University of New South Wales in Australia, agreed that higher prevalence of HCV infection and greater transmission risk following an injection with a contaminated syringe as compared to HIV have hampered harm reduction measures. They also noted that current implementation of harm reduction measures in most settings is inadequate. Rates of equipment sharing remain high, and access to opioid substitution therapy and other drug treatment programs is limited.

The editorial authors also pointed out the impact that an HCV vaccine could have on new cases of HCV infection. Though a highly efficacious vaccine has not yet been discovered, efforts to do so are crucial. They suggested that even though the window for preventing HCV may be small, improvements in HCV prevention are feasible.

New probiotic combats inflammatory bowel disease
Probiotic offers possibility of safe, drug-free treatment

CHICAGO — You know the probiotics in your peach yogurt are healthful, but now it appears they may also be a powerful treatment for disease.

A genetically tweaked version of a common probiotic found in yogurt and cheese appears to be an effective therapy for inflammatory bowel diseases such as Crohn's disease and ulcerative colitis. It may also prove to be useful in colon cancer, another disease triggered by inflammation.

Northwestern Medicine researchers deleted a gene in the probiotic Lactobacillus acidophilus and fed the new form to mice with two different models of colitis. After 13 days of treatment, the novel probiotic strain nearly eliminated colon inflammation in the mice and halted progression of their disease by 95 percent.

"This opens brand new avenues to treat various autoimmune diseases of the gut, including inflammatory bowel disease and colon cancer, all which can be triggered by imbalanced inflammatory immune responses," said Mansour Mohamadzadeh, associate professor of medicine at Northwestern University Feinberg School of Medicine and lead investigator of the study. He also is a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

The study will be published Jan. 31 in the Proceedings of the National Academy of Sciences.

While the origin of these bowel diseases is not known, Crohn's disease and ulcerative colitis are two chronically relapsing diseases in which sufferers have an ongoing tissue inflammation that alters the functioning of the intestine. The diseases affect more than 1 million people in the United States and can...
cause weight loss, diarrhea, abdominal pain and cramping and gastrointestinal bleeding. Current drug treatment is not completely effective and patients can relapse, Mohamadzadeh said.

"Such gene targeting in a probiotic bacteria such as Lactobacillus acidophilus offers the possibility of a safe, drug-free treatment in the near future," he said.

In the study, the modified Lactobacillus acidophilus entered the gut, which is akin to a battlefield of friendly fire with immune cells attacking the intestine. The Lactobacillus acidophilus acted as the gut’s peacekeeping force, calming the overstimulated immune cells.

The probiotic restored intestinal peace by mobilizing messenger immune cells, called dendritic cells. The dendritic cells, in turn, enhanced the production of other functional immune cells, regulatory T-cells that rebalanced intestinal and systemic inflammation.

"They essentially calm everything down and restore it to normal," Mohamadzadeh explained. The next step will be a clinical trial with the new form of Lactobacillus acidophilus.

Mohamadzadeh and his colleagues at the Lurie Cancer Center are currently researching the effect of the new Lactobacillus acidophilus on colon cancer.