October 2010 Epidemics and AIDS Update

1. Detectable genital HIV shedding associated with cervical infections appears minimal among women taking ART
2. More Activists Band Together to Fight Child Sex Trafficking
3. South African AIDS Orphans Aging
4. Alberta Neurologist's Study Suggests HIV Can Cause Brain Disease
5. HIV/AIDS Activists: 'Let's Talk About Sex, It's Killing Us'
6. Early Antiretroviral Treatment Can Help Preserve B-Cell Immune Function
7. Research identifies a new bacterial foe in CF
8. New study highlights sexual behavior, condom use by US individuals ages 14 to 94
9. Possible Method for Boosting the Immune System to Protect Infants Against HIV
10. How Salmonella Bacteria Spread in Humans
11. HIV-Positive Mothers Not Convinced to Exclusively Breastfeed
12. HIV Testing Preferences Among Young Men of Color Who Have Sex with Men
13. Neonatal Circumcision Yet to Gain Ground
14. Failing to Control Tuberculosis
16. Symptoms still common in patients with HIV, and associated with poor adherence and risky sex
17. Immune system linked with accumulation of toxic tau protein
18. One lock, many keys
19. New Sex Education Funding Ends Decade of Abstinence-Only
20. HIV a Threat to Those Age 50 and Older
21. Modelling study: no condom use after recent viral load test safer than intermittent condom use
22. HIV infections could hit 3.2m a year by 2031 if funding is not increased
23. Study Sheds Light on How HIV Evades Immune Response
24. Bridging the Gap: Using School-Based Health Services to Improve Chlamydia Screening Among Young Women
25. Studying Illnesses Caused by Worms
26. Yersinia Pestis Bacteria Confirmed as Cause of Middle Ages 'Black Death' Plague Epidemic
27. Bacteria Can Stand Up and 'Walk'
28. Melanoma Uses Body's Immune System to Spread to Lungs
29. How Bacteria Become Resistant to Antibiotics
30. Insulin is key to kidney disease
31. Rare Hybrid Cell Key to Regulating the Immune System
32. Cell Survival Protein Discovery Rewrites Immune System Story
33. New Survey on Sex in US, Biggest Since 1994
34. Australian Men's Sexual Practices in Saunas, Sex Clubs and Other Male Sex on Premises Venues
35. Work Needed To Maintain Fight Against Polio In Nigeria
36. NIAID Awards Grant For Development Of Needle-Free Dengue Vaccine
37. New River Blindness Diagnostic Test Developed
38. Calif. porn actor tests positive for HIV
39. Uganda: Nation to Produce New HIV Drug
40. China court hears first HIV discrimination suit
41. Condom Negotiation Strategies and Actual Condom Use Among Latino Youth
42. Reducing HIV Risk Behavior of Men Who Have Sex with Men Through Persuasive Computing: Results of the Men's Internet Study-II
43. West African Cholera Epidemic Exacerbated By Flooding; More Than 1,800 Deaths Reported
44. A crucial link in immune development and regulation unearthed
45. Adding drugs to already successful HIV treatment doesn't reduce viral load further
46. MTV's '16 and Pregnant' Series Hailed a Cold Shower for Teens
47. Prevalence of Sexually Transmitted Infection/Human Immunodeficiency Virus Counseling Services Received by Teen Males, 1995-2002
48. Trends in the Location of the HIV-Positive Population in Australia: Implications for Access to Health Care Services and Delivery
49. Highly Pathogenic Bird Flu Virus Can Survive Months on Steel or Glass at Cooler Temperatures
50. Virus Deadly in Livestock Is No More, U.N. Declares
51. Scientist as subject
52. NIH Scientists Researching HIV Vaccine Develop Method for Preserving Virus Fragment Shape
53. Dr. James’s Fever Powder, circa 1746
54. 1 in 22 Blacks Will Get HIV, CDC Report Says
55. New HIV Cases Top One Thousand Again
56. Interventions for Young People in Australia to Reduce HIV and Sexually Transmitted Infections: A Systematic Review
57. Analysis indicates a third H1N1 pandemic wave unlikely in 2010
58. Attack on C. difficile: How can we combat this serious health issue
59. Mystery Solved: How Genes Are Selectively Silenced
60. The Return of Mad Cow Disease?
61. NeurogesX to Pursue Expanded U.S. Label for Qutenza® (capsaicin) 8% Patch in HIV-Associated Neuropathy
62. Fed OKs Vivitrol to Treat Heroin, Narcotic Addictions
63. Ten Years Fighting HIV/AIDS and Reaching Out to Gays
64. Smoking-Related Health Risks Among Persons with HIV in the Strategies for Management of Antiretroviral Therapy Clinical Trial
65. Connecting Discovery and Delivery: The Need for More Evidence on Effective Smoking Cessation Strategies for People Living with HIV/AIDS
66. Antiretroviral Therapy Did Not Reduce HIV Transmission within Serodiscordant Couples in China
67. Intestinal Enzyme Helps Maintain Population of Beneficial Bacteria
68. Gut Microbes Promote Cell Turnover by a Well-Known Pathway
69. Africa: Botswana Ex-President in Plea Over Homosexuals
70. Zambia: Criminalising HIV Transmission
71. Gays in Uganda say they’re living in fear
72. Sterilizing with fluorescent lights
73. No Standard for the Placebo?
74. Improved Antibiotic Coatings: Research Aims to Make Medical Devices Safer by Preventing Biofilms
75. HIV transmitted during a knife attack
76. Drug safety bodies issue warning on heart rhythm risks with saquinavir (Invirase)
77. SOUTH AFRICA: Research shows World Cup did not fuel sex work or HIV
78. FDA Warns of Heart Risk with HIV Drug Combination
79. Southern Africa Life Expectancy Rising Slightly: UN
80. TB Cases Decline, but Drug-Resistant TB Now a Risk
81. Hepatitis C Virus Can Damage Brain Cells
82. Helena School Board OK’s Revised Sex Education Plan
83. Study Uncovers Structure of CXCR4 Co-receptor Used by HIV to Enter Cells
84. Phase 2 Trial Tests Intensified Antiretroviral Therapy plus Interleukin-7 for HIV Eradication
85. Intensification of Antiretroviral Therapy Does Not Eliminate HIV in Gut or Central Nervous System
86. Cholera Kills 138 People, More Than 1,500 Other Cases Reported, Haitian Health Ministry Officials Say
87. Researchers Find Evidence That A. Gambiae Mosquito Is Evolving Into Two Strains, Could Present Challenges For Malaria Control Efforts
88. Iowa State, Ames Lab chemists discover proton mechanism used by flu virus to infect cells
89. How H1N1 differs from other viruses as a respiratory illness
90. Swine flu variant linked to fatal cases might have disabled the clearing mechanism of lungs, study suggests
91. Mount Sinai researchers discover origin of immune cells in the brain
92. Natural Killer Cells May Limit Inflammation in the Central Nervous System
93. Brain cell origin solved
94. Templates for a vaccine?
95. Giant marine virus found
96. New model shows future impact of circumcision on Africa’s HIV epidemic probably underestimated
97. Swiss drug policy should serve as model: experts
98. Researchers Shed Light on HIV Gag Protein Required for Viral Assembly
99. Reduction of Latent HIV Reservoir Does Not Prevent Viral Rebound after Stopping Antiretroviral Therapy
100. Bivalent Oral Polio Vaccine Produces Better Immune Response Than Trivalent Vaccine, Study Says
101. A new player in the innate immunity game?
102. ‘Reaper’ Protein Strikes at Mitochondria to Kill Cells
103. Immune Cells Deploy Traps to Catch and Kill Pathogens
104. Molecular Guardian of Cell’s RNA Identified
105. 1000 Genomes Project publishes analysis of completed pilot phase
106. Homosexuals Contribute 30% Of New HIV Infections In Kenya – NASCOP
107. Eve of an HIV Epidemic in Romania
Detectable genital HIV shedding associated with cervical infections appears minimal among women taking ART
Kelly Safreed-Harmon
Published: 01 October 2010
Results from a small Kenyan study suggest that cervical HIV viral load levels remain low during episodes of cervical infection in HIV-positive women taking antiretroviral therapy (ART).

The finding is of interest to researchers exploring the dynamics of HIV infectiousness in the context of the global scale-up of ART, since viral load reductions resulting from ART usage in some settings may be of a large enough magnitude to bring about population-level reductions in HIV transmission.

Although ART greatly lowers infectiousness overall, detectable levels of HIV persist in the genital secretions of a small proportion of women taking ART.

The fact that cervical infections can increase genital HIV shedding in women not taking ART raises the question of whether the same dynamic might continue operating to some degree in women after they initiate treatment.

The Kenyan study indicates that this is not generally the case. Most study participants who developed cervical infections while taking ART were found to maintain undetectable cervical HIV viral load levels during those episodes. Among the small number of women whose viral load levels surpassed the threshold of detection, viral load levels still remained quite low.

The prospective cohort study enrolled 147 HIV-positive Kenyan women who met standard clinical criteria for ART initiation. The women began taking standard first-line antiretroviral regimens and providing biological samples for monthly viral load and genital infection testing. The viral load threshold of detection was 100 copies/mL.

Researchers analysed data from 30 study participants who experienced 31 episodes of cervical infection at least one month after they had started ART. One case involved the diagnosis and treatment of chlamydia; 17, gonorrhea; and 13, non-specific cervicitis.

From a statistical standpoint, women’s likelihood of developing detectable HIV viral load levels increased with the onset of cervical infections. However, only five women actually had detectable viral load levels and cervical infections concurrently.

The women’s viral load levels ranged from 100 to 820 copies/mL during episodes of cervical infection (median, 115 copies/mL).

The median age of the study subset experiencing cervical infections was 36 (interquartile range, 31 – 38). ART pill counts indicated high treatment adherence levels.

The authors caution that although their results “further highlight the potential benefits of ART as a prevention strategy,” it is important to bear in mind that even low levels of HIV in genital secretions can potentially result in transmission to sexual partners.

Thus, the paper concludes, “identification and treatment of cervical infections may help to optimize the secondary [HIV] prevention benefits of ART.”

The Kenyan study, although too small to yield definitive findings, contributes another piece to the complex picture that is emerging in relation to the concept of HIV treatment also functioning as an HIV prevention tool.

If other researchers concur that cervical infections do not greatly increase HIV-positive women’s likelihood of transmitting the virus to sexual partners, then this can be ruled out as a potential factor in efforts to explain why some people on ART are at greater risk of transmitting the virus onward than are others.

Reference

More Activists Band Together to Fight Child Sex Trafficking
USA Today, (09.30.2010) Wendy Koch
Twenty-two state attorneys general have joined in calling on the classified-ad website Backpage.com to shutter its adult-services section, following successful pressure on Craigslist.com to do the same. The push
is part of a growing movement among women's groups, state officials, human rights activists, and
celebrities to crack down on child sex trafficking.

“Adult-services sections are little more than online brothels,” said Connecticut Attorney General
Richard Blumenthal, in announcing the appeal to Backpage.com, which is owned by Village Voice Media.
Craigslist eliminated its adult-services ads on Sept. 3.

The Women's Funding Network, which helps abused women, financed a study of three states where it
is fighting the problem—New York, Michigan, and Minnesota—and found the number of girls trafficked
through online classified ads and escort services rose by at least 20 percent from February through
August. The National Center for Missing & Exploited Children estimates that each year more than
100,000 US children are victimized, often starting at ages 11 to 14, by criminal networks.

“These children have been traumatized, brainwashed, and abandoned and need specialized resources

In an online response, Backpage said it “respectfully declines the recent demand.” Attorneys general
are transferring the blame “from criminal predators to a legal business operator in an apparent attempt
to capitalize on political opportunity,” the statement said.

On Sept. 15, Craigslist executive William “Clint” Powell told the House Judiciary Committee that
stopping the ads will harm efforts to eradicate child trafficking. “Those who formerly posted adult-
services ads on Craigslist will now advertise at countless other venues,” he said, adding that the site
worked with police and turned over the credit card information of people accused of crimes.

South African AIDS Orphans Aging

A growing number of South African AIDS orphans are in need of specialized care as they transition to
adulthood, a new Institute for Democracy in South Africa (IDASA) study finds.

South Africa has the world’s largest HIV/AIDS caseload and is home to nearly 3 million orphans,
many of whom lost parents to AIDS. According to IDASA, an estimated 280,000 South African children
age 15 or younger are HIV-positive. With free antiretroviral drugs available through the public health
system, many HIV-positive orphans who previously would not have been expected to live to adolescence
are reaching college age.

HIV-positive orphans need support with sexual issues and access to free education, health care, and
training opportunities, said Marietjie Oelofsen, manager of IDASA’s Government and AIDS program.

Harry Moultrie of Johannesburg-based Enhancing Children’s HIV Outcomes, an agency that consults
with the health department, said HIV-positive teens sometimes assert their independence in self-
destructive ways, including not adhering to their HIV medicines. “The health care system is not well-
structured to meeting the needs of these adolescents,” he said.

Sibani Mngadi, spokesperson for the Ministry of Women, Children, and Persons with Disabilities,
acknowledged that the government must do more to assist teen orphans as they grow up. Although AIDS
orphans receive financial assistance from the government until they reach 18, there is a growing
realization that they need more specialized attention as they become young adults.

Heartbeat, a government-funded group that provides after-school programs to 4,000 AIDS orphans,
is doing just that. At community centers, many located in townships, the children sit in circles, discussing
their problems and aspirations. Heartbeat offers career counseling, guidance on sex and drugs, and sports
opportunities.

Alberta Neurologist’s Study Suggests HIV Can Cause Brain Disease

Despite the availability of antiretroviral (ARV) therapy, neurologic disorders occur frequently in
HIV/AIDS patients and increase the risk of death, a study in Canada finds. This may reflect late diagnosis
and entry into care, so efforts to identify people with HIV earlier are vital, AIDS expert Dr. Julio Montaner
said.

Researchers examined 1,651 HIV-positive patients receiving care at the Southern Alberta Clinic from
1998 to 2008. Of them, 404 (24.5 percent) had one or more neurologic disorders, and 41 percent of
people with AIDS exhibited neurologic disease.

Most prevalent were symptomatic distal sensory polyneuropathy (10 percent) and HIV-associated
neurocognitive disorder (HAND, 6.2 percent), wrote Dr. Chris Power, a professor at the universities of
Alberta and Calgary, and colleagues.
Patients with at least one neurologic disorder exhibited higher mortality rates (17.6 percent vs. 8 percent, \( p<0.0001 \)), and especially AIDS-related deaths (9.7 percent vs. 3.2 percent, \( p<0.0001 \)), compared with those without neurologic disorders.

The mortality hazard ratio was calculated by Cox proportional hazard models and adjusted for demographic and clinical variables. The highest mortality hazard ratio was associated with opportunistic infections of the central nervous system, (HR 5.3, 95 percent confidence interval [CI] 2.5-11.2), followed by HAND (HR 3.1, 95 percent CI 1.8-5.3) and any neurologic disorder (HR 2.0, 95 percent CI 1.2-3.2).

“It’s actually quite disturbing in the sense that he’s reporting a significant number of people who are presenting with neurological disease related to HIV,” said Montaner, director of the British Columbia Center for Excellence in HIV/AIDS. “An astonishing amount of the pathology that is being presented is actually preventable if we implement an aggressive strategy of what we call seek and treat.”

Power said the problem may be that ARVs do not make it through to the nervous system in sufficient amounts to offset the consequences of HIV on the brain. Only a fraction makes it through, he said, noting that some are better than others. One solution might be to fine-tune existing therapies in order to enhance levels in the nervous system, he said.


HIV/AIDS Activists: 'Let’s Talk About Sex, It’s Killing Us'

Black Voices News (Riverside), (09.15.2010) Chris Levister

At a Sept. 10 health summit at Community Hospital of San Bernardino, HIV/AIDS activist Carla Bailey told attendees “the HIV fight begins and ends with us.”

“De-nial is not just a river in Egypt,” said Bailey. “We know firsthand what HIV/AIDS is doing to the black community. We’ve buried countless family members, neighbors, and friends, yet every day people get infected with the virus. How do you tackle this epidemic when a lot of people are reluctant and embarrassed about discussing AIDS?”

The 3rd annual HIV/AIDS Health Summit, titled “What’s Killing Us?”, was sponsored by B.A.S.I.A (Brothers and Sisters in Action). More than 100 health professionals and persons living with the disease attended the forum.

As a volunteer and full-time activist, Bailey travels the country educating young people about HIV/AIDS. She has addressed women’s conferences, church groups, and legislators, and has appeared on NPR, C-SPAN, Women’s Network TV, and other media outlets.

According to Bailey, two huge HIV myths persist in the African-American community. The first is there is a vaccine or cure for HIV/AIDS, “but they’re not telling us because it’s a government plot to kill black people. The second is, ‘you can take medicine for HIV and look like Magic Johnson.’”

“There is a climate of ignorance that blames everything from government conspiracy to punishment from God,” said Dr. Wilbert C. Jordan, a Los Angeles-based physician and a leading researcher on HIV/AIDS in the African-American community. The best way to overcome myths and misinformation is for blacks to educate themselves about the virus, its consequences, and the resources available, he said.

Early Antiretroviral Treatment Can Help Preserve B-Cell Immune Function

**SUMMARY:** People with HIV have lower levels of antibody-producing B-cells than HIV negative individuals, but numbers rise significantly after initiation of effective antiretroviral therapy (ART), according to a study published in the September 13, 2010 advance online edition of Blood. What’s more, people at an early stage of HIV infection had more fresh B-cells and achieved full recovery, while those with chronic infection had more immature or exhausted cells and did not reach normal levels, suggesting it may be beneficial to start ART sooner, while B-cell immune function is still relatively well preserved.

Below is the text of a media advisory issued by the National Institute of Allergy and Infectious Diseases describing the study findings.

**NIH Scientists Find More Health Benefits From Starting HIV Treatment Early**

Bethesda, MD—September 28, 2010—HIV-infected individuals who begin antiretroviral therapy (ART) soon after acquiring the virus may have stronger immune responses to other pathogens than HIV-infected individuals who begin ART later, a new study from the National Institutes of Health has found. This finding suggests that early initiation of ART may prevent irreversible immune system damage and adds to the body of evidence showing significant health benefits from early ART.

Scientists from the National Institute of Allergy and Infectious Diseases, part of NIH, measured the quantity and qualities of B cells in blood samples taken from three groups of study volunteers: men who had been infected with HIV for fewer than 6 months; men who had been infected with HIV for 6 months
or more (often for several years); and men who were not infected with HIV. The HIV-infected men began taking ART for the first time once they entered the study.

B cells make proteins called antibodies that can flag pathogens for destruction by the immune system and prevent them from infecting cells. At the outset of the study, the number of B cells in the blood of both groups of HIV-infected men was significantly lower than the number of B cells in the blood of the uninfected men. Once the two groups of HIV-infected men began ART, however, the numbers of B cells in their blood increased significantly and to similar degrees.

Qualitatively, however, the compositions of B cells in the two groups of HIV-infected men differed notably throughout the study. The researchers compared the relative proportions of six different types of B cells within and among each of the three groups at the study outset and one year after the HIV-infected men had started ART. The scientists observed that early treatment restored resting memory B cells to the same level as that in HIV-uninfected men, but late treatment did not. Resting memory B cells remember how to make antibodies to a pathogen and can last a lifetime. Also, early ART reduced the proportion of immature B cells to the same level as that in HIV-uninfected men, but late treatment did not. In addition, after one year, the late treatment group had a significantly greater proportion of so-called exhausted B cells—those that have shut themselves off and resist doing their usual pathogen-fighting activities—impaired with the other two groups of participants.

To learn how these differences affected immune system responses to new infections, the research team examined how the two groups of HIV-infected men responded to influenza vaccination at the start of the study and one year after beginning treatment. At the one-year point, a significantly greater proportion of B cells made anti-influenza antibodies in the early treatment group compared with the late treatment group. This suggests that starting ART early in the course of HIV infection enables individuals to fight off other pathogens better than if they start ART later, when the infection has become chronic.

Reference

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Research identifies a new bacterial foe in CF

Exacerbations in cystic fibrosis (CF) may be linked to chronic infection with a bacterium called *Stenotrophomonas maltophilia*, which was previously thought to simply colonize the CF lung. The finding that chronic infection with *S. maltophilia* is independently linked with an increased risk of exacerbations gives clinicians and researchers a new potential measure of the health status of CF patients, as well as a new potential target in fighting their disease.

The findings were published online ahead of the print edition of the American Thoracic Society’s American Journal of Respiratory and Critical Care Medicine.

"Our study showed that chronic infection with *S. maltophilia*, which was previously not regarded as prognostically significant, may have a real impact on the progression of CF in patients,” said Valerie Waters, M.D., assistant professor of infectious diseases at the Hospital for Sick Children in Toronto. "We hope that this study is a starting point for further research, which may point to therapeutic possibilities associated with controlling these infections."

CF is a congenital disease that is characterized by thick, sticky mucus in the lungs and digestive tract, leading to chronic infections and shortened life. Over time, exacerbations in CF can lead to permanent loss of lung function, thus driving the progression of this deadly disease.

About one in 31,000 people are born with CF, and there is no cure, although new treatments have dramatically improved and extended the lives of CF patients in recent decades. At present, the average lifespan of a CF patient is 35 years.

As CF patients are living longer than ever before, respiratory tract colonization and infection with multi-drug resistant pathogens are increasing in frequency. Among these, *S. maltophilia* is particularly common and is isolated from the respiratory tract of up to a third of CF patients. To assess whether *S. maltophilia* represented a true infection, rather than merely a colonizing organism, and whether it had an impact on the progression of disease, Dr. Waters and colleagues performed a two-stage study. In the first stage, they sought to determine if *S. maltophilia* generated an immune response in CF patients. In the second stage, they retrospectively followed almost 700 CF patients for 12 years to determine whether chronic infection with *S. maltophilia* was independently associated with an increased risk of exacerbation or lowered lung function.

They found that antibody levels to *S. maltophilia* flagellin, were about two times higher in chronically infected patients compared to those who were never infected, indicating a specific immune response and a
true infection, rather than mere colonization. The increased antibody levels were also associated with lower lung function, as measured by FEV1 (forced expiratory volume in one second.)

Furthermore, they found that patients with chronic *S. maltophilia* infections had a 63 percent greater risk of exacerbations than those who had never been infected, although there were no significant differences detected in the rate of lung function decline.

"This is the first study to our knowledge that demonstrates CF patients with chronic *S. maltophilia* infection have a specific immune response, which is in turn associated with lower lung function," said Dr. Waters. "There have been few studies that investigate the effect of *S. maltophilia* infection on clinical outcomes; those that have been short-term and have not shown any significant clinical effects of the infection. This study, however, points to the possibility that chronic infection has a real and significant clinical impact on these patients."

While the length of the study may not have been sufficient to determine any possible differences in lung function between chronically infected CF patients and those who were intermittently or never infected, Dr. Waters points out that these effects may in fact occur, possibly in younger patients.

"It is crucial that we look to determine whether chronic *S. maltophilia* infection directly results in the worsening of lung function," she said. "We plan to investigate the effects of chronic *S. maltophilia* during pulmonary exacerbations in future studies."

**New study highlights sexual behavior, condom use by US individuals ages 14 to 94**

BLOOMINGTON, Ind. — Findings from the largest nationally representative study of sexual and sexual-health behaviors ever fielded, conducted by Indiana University sexual health researchers, provides an updated and much needed snapshot of contemporary Americans' sexual behaviors, including a description of more than 40 combinations of sexual acts that people perform during sexual events, patterns of condom use by adolescents and adults, and the percentage of Americans participating in same-sex encounters.

The National Survey of Sexual Health and Behavior (NSSHB) was conducted by researchers from the Center for Sexual Health Promotion (CSHP) in Indiana University's School of Health, Physical Education, and Recreation (HPER).

The NSSHB is one of the most comprehensive studies on these topics in almost two decades and documents the sexual experiences and condom-use behaviors of 5,865 adolescents and adults ages 14 to 94.

Initial findings from the survey, presented in nine separate research articles, were published on Oct. 1 in a special issue of The Journal of Sexual Medicine, a leading peer-reviewed journal in the area of urology and sexual health. The issue also includes commentaries offering perspectives on the study from leading U.S. sexual health authorities, including former U.S. Surgeon General Dr. Joycelyn Elders, Dr. Kevin Fenton, Director of the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention at the national Centers for Disease Control and Prevention (CDC), and Lynn Barclay, President and CEO of the American Social Health Association.

"This survey is one of the most expansive nationally representative studies of sexual behavior and condom use ever conducted, given the 80-year span of ages," said Michael Reece, director of the Center for Sexual Health Promotion. "These data about sexual behaviors and condom use in contemporary America are critically needed by medical and public health professionals who are on the front lines addressing issues such as HIV, sexually transmissible infections and unintended pregnancy."

According to the study's findings, one of four acts of vaginal intercourse are condom protected in the U.S. (one in three among singles).

"These data, when compared to other studies in the recent past, suggest that although condom use has increased among some groups, efforts to promote the use of condoms to sexually active individuals should remain a public health priority," Reece said.

Researchers believe the findings will be of interest to the general public, as well as to health professionals.

"People are often curious about others' sex lives," said Debby Herbenick, associate director of the CSHP. "They want to know how often men and women in different age groups have sex, the types of sex they engage in, and whether they are enjoying it or experiencing sexual difficulties. Our data provide answers to these common sex questions and demonstrate how sex has changed in the nearly 20 years since the last study of its kind."
Herbenick said the study helps both the public and professionals to understand how condom use patterns vary across these different stages in people's relationships and across ages, adding that "findings show that condoms are used twice as often with casual sexual partners as with relationship partners, a trend that is consistent for both men and women across age groups that span 50 years."

The survey indicates that there is enormous variability in the sexual repertoires of U.S. adults now, and adult men and women rarely engage in just one sex act when they have sex. While vaginal intercourse is still the most common sexual behavior reported by adults, many sexual events do not involve intercourse and include only partnered masturbation or oral sex. When it comes to responsible sexual behaviors, condom use is higher among black and Hispanic Americans than among white Americans and those from other racial groups.

A unique feature of the study was the inclusion of adolescent men and women. Dennis Fortenberry, M.D., professor of pediatrics in the IU School of Medicine, led the adolescent aspects of the study. "Many surveys of adolescent sexual behavior create an impression that adolescents are becoming sexually active at younger ages, and that most teens are sexually active," Fortenberry said. "Our data show that partnered sexual behaviors are important but by no means pervasive aspects of adolescents' lives. In fact, many contemporary adolescents are being responsible by abstaining or by using condoms when having sex."

Additional key findings highlighted in the collection of papers include:

- There is enormous variability in the sexual repertoires of U.S. adults, with more than 40 combinations of sexual activity described at adults' most recent sexual event.
- Many older adults continue to have active pleasurable sex lives, reporting a range of different behaviors and partner types, however adults over the age of 40 have the lowest rates of condom use. Although these individuals may not be as concerned about pregnancy, this suggests the need to enhance education efforts for older individuals regarding STI risks and prevention.
- About 85 percent of men report that their partner had an orgasm at the most recent sexual event; this compares to the 64 percent of women who report having had an orgasm at their most recent sexual event. (A difference that is too large to be accounted for by some of the men having had male partners at their most recent event.)
- Men are more likely to orgasm when sex includes vaginal intercourse; women are more likely to orgasm when they engage in a variety of sex acts and when oral sex or vaginal intercourse is included.
- While about 7 percent of adult women and 8 percent of men identify as gay, lesbian or bisexual, the proportion of individuals in the U.S. who have had same-gender sexual interactions at some point in their lives is higher.
- At any given point in time, most U.S. adolescents are not engaging in partnered sexual behavior. While 40 percent of 17 year-old males reported vaginal intercourse in the past year, only 27 percent reported the same in the past 90 days.
- Adults using a condom for intercourse were just as likely to rate the sexual extent positively in terms of arousal, pleasure and orgasm than when having intercourse without one.

Possible Method for Boosting the Immune System to Protect Infants Against HIV

ScienceDaily (Oct. 3, 2010) — Researchers at Oregon Health &Science University may have uncovered a new weapon for combating HIV as it is passed from mother to newborn child. The research, which was led by researchers at OHSU's Oregon National Primate Research Center, will be published in the October 3rd online edition of the journal Nature Medicine.

"Mother-to-infant transmission of HIV is a tremendous worldwide problem, especially in several African nations," said Nancy Haigwood, Ph.D., researcher and director of the Oregon National Primate Research Center at OHSU.

According to the latest data from the World Health Organization, 33.4 million people were infected by the virus in 2008. About 67 percent of the world's infections are in African countries. In addition, 91 percent of the world's childhood infections are in Africa.

Haigwood, her colleagues at OHSU, along with researchers at the University of Washington are investigating strategies for preventing or countering HIV infections in babies born to women with HIV. Their strategy: to educate part of the baby's immune system within the first few hours of birth to better fight of the disease.
"HIV attacks and kills T-cells, the white blood cells that play an important role in the immune system because they have the ability to identify and destroy disease invaders. By attacking the body's natural defenses, the disease progresses, causes AIDS and eventually death," explained Haigwood. "Therefore, many therapies focus on protecting T-cells."

However, Haigwood and her colleagues took a different approach. They focused on another component of the immune system, which was initially thought to play a lesser role in the body's defense against HIV. Babies born to HIV-infected mothers have HIV-specific neutralizing antibodies at the time of birth that are "passively" acquired across the placenta. They wanted to determine whether boosted neutralizing antibody levels would weaken the disease's ability to overtake the body's defenses.

To investigate this possible treatment, the researchers studied three small groups of infant monkeys. The first group was given additional antibodies derived from healthy mothers. The second group was given antibodies matched to simian/human immunodeficiency virus (SHIV). SHIV is a hybrid virus used in research to ensure that results translate between species. The third group of animals was provided with HIV antibodies similar to, but not exactly matching, the strain of infection they would receive. The three groups were then exposed to SHIV and their immune systems were subsequently monitored.

Unlike the other two groups, the "HIV-matched" animals were better protected from the virus. They developed higher levels of neutralizing antibodies and, had lower levels of SHIV in their blood plasma than the comparison groups six months post-infection. In addition they maintained their CD4+ T cells—another component of the immune system.

The study also provided insights into the level of antibodies needed to impact disease progression. For this study, the antibody levels were relatively low dosed. Previously, antibodies were shown to block infection in animal models. This study demonstrated, for the first time, that very low levels of antibodies too low to block infection can influence disease progression in this setting and stimulate an immune response that contributes to viral control in the absence of drug treatment.

In future studies, the researchers hope to learn whether higher doses of antibodies translate into greater protection for the infants.

"This research demonstrates that boosting the body's HIV antibodies by a time-honored method of passive transfer that would use new HIV-specific human monoclonal antibodies may be a strategy for reducing infection levels and protecting CD4+ T cells in newborn children," said Haigwood. "While the treatment would not likely prevent infection, it could limit the levels of infection in children which would greatly reduce suffering and extend lives."

Journal Reference:
Cherie T Ng, J Pablo Jaworski, Pushpa Jayaraman, William F Sutton, Patrick Delio, LaRene Kuller, David Anderson, Gary Landucci, Barbra A Richardson, Dennis R Burton, Donald N Forthal & Nancy L Haigwood. Passive neutralizing antibody controls SHIV viremia and enhances B cell responses in infant macaques. Nature Medicine, 03 October 2010 DOI: 10.1038/nm.2233

How Salmonella Bacteria Spread in Humans
ScienceDaily (Sep. 30, 2010) — New findings by National Institutes of Health scientists could explain how Salmonella bacteria, a common cause of food poisoning, efficiently spread in people. In a study published this week in the Proceedings of the National Academy of Sciences, researchers describe finding a reservoir of rapidly replicating Salmonella inside epithelial cells. These bacteria are primed to infect other cells and are pushed from the epithelial layer by a new mechanism that frees the Salmonella to infect other cells or be shed into the intestine.

The Centers for Disease Control and Prevention estimate that Salmonella infections sicken 40,000 people each year in the United States, though the actual number of infections is likely much higher because many cases are mild and not diagnosed or reported. Currently, Salmonella is the focus of an ongoing U.S. public health investigation into contaminated chicken eggs.
"Unfortunately, far too many people have experienced the debilitating effects of Salmonella, which cause disease via largely unexplained processes, including overactive inflammatory responses," says Anthony S. Fauci, M.D., director of NIH’s National Institute of Allergy and Infectious Diseases (NIAID). "This elegant study provides new insight into the origins of that inflammatory disease process."

While much is known about the human infectious cycle of Salmonella, scientists have yet to understand how the bacteria escape the gut to spread infection. Epithelial cells line the outer and inner surfaces of the body, such as the skin and gut, and form a continuous protective tissue against infection. But Salmonella have learned how to live inside epithelial cells and use them for their benefit. Salmonella protect themselves within special membrane-bound compartments, called vacuoles, inside gut epithelial cells.

Using special high-resolution microscopes to view laboratory-grown human intestinal epithelial cells and laboratory mice infected with Salmonella, an NIAID research group led by Olivia Steele-Mortimer, Ph.D., in collaboration with Bruce Vallance, Ph.D., of the University of British Columbia in Vancouver, discovered a secondary population of Salmonella not confined within a vacuole, but instead moving freely inside the epithelial cells. This reservoir of Salmonella is distinct from vacuolar Salmonella. The bacteria multiply much faster; they have long tail-like projections, called flagella, used to move; and they exhibit a needle complex they use to pierce cells and inject their proteins. With these attributes, this population of Salmonella is genetically programmed to invade new cells.

The scientists observed that epithelial cells containing the hyper-replicating, invasive Salmonella are eventually pushed out of the intestinal tissue into the gut cavity, setting the Salmonella free. The mechanism used to push these Salmonella-infected cells into the body cavity resembles the natural mechanism humans use to shed dying or dead epithelial cells from their gut. The scientists believe that Salmonella have hijacked this mechanism to facilitate their own escape.

The human immune system, however, also senses that these are not normal, dying cells in the gut and triggers a response that includes release of interleukin-18, a small protein that sets off an inflammation cascade. Interleukin-18 also is prominent in chronic intestinal inflammation associated with autoimmune disorders, such as inflammatory bowel disease. The effects of interleukin-18 release provide an explanation for the acute intestinal inflammation associated with Salmonella infections.

The scientists hope their research leads to a treatment that prevents the spread of infection. They are focusing on how this specialized population of Salmonella escapes from its membrane-bound compartment to multiply and swim freely in the cell.

Journal Reference:

HIV-Positive Mothers Not Convinced to Exclusively Breastfeed

Inter Press Service, (09.01.2010) Alina Balopi

Conditions on the ground in Botswana could thwart updated World Health Organization (WHO) guidelines, which recommend that new mothers with HIV breastfeed their infants, provided either or both are on antiretroviral (ARV) therapy, until at least the infant’s first birthday.

Influencing the WHO decision was the randomized study by the Botswana-Harvard Partnership (BHP). In it, HIV-positive pregnant women in Botswana were given ARVs at 28 weeks of pregnancy, and they were told to breastfeed exclusively while taking ARVs until the infant was weaned at six months. The mother-to-child transmission rate was 1 percent.

“The [WHO] recommendations have not been instilled in government medical institutions, and I doubt it would be because it is not practical,” said Dr. Unabatšho Maposa of the Princess Marina Referral Hospital. “The baby should not be given any other liquids except the mother’s milk. Therefore, there is no woman who can do that because they are bound to give the baby something, and that is when it becomes dangerous for the baby.”

However, Botswana’s current protocol discouraging HIV-positive mothers from breastfeeding has its own dangers, said Dr. Joseph Makhema, BHP’s project director.

“Currently, the protocol has been that women on treatment could not breastfeed their babies, while the babies had to take one month treatment while feeding on formula,” Makhema said. “This exposes children to illnesses as the formula is not always prepared well or the bottles got exposed to infections.”

And due to occasional formula shortages, Makhema noted it is “necessary to find a method that would be affordable and sustainable to control transmission of the virus from mothers to babies.”
Botswana’s Ministry of Health is drafting domestic guidelines and will disseminate them for implementation when they are finalized, said Koona Keapoletswe, acting director of the ministry’s HIV/AIDS department.

**HIV Testing Preferences Among Young Men of Color Who Have Sex with Men**

*American Journal of Public Health Vol. 100; No. 10: P. 1961-1966, (10..2010) Alwyn Cohall, MD; Shelia Dini, MPH; Andrea Nye, MPH, MBA; Bonne Dye, MPH; Natalie Neu, MD, MPH; Christel Hyden, MS, CHES*

Awareness of and preferences for rapid HIV testing among young men of color who have sex with men and are engaged in high-risk HIV behaviors were assessed in the current report. The cross-sectional study of 177 young MSM was performed in New York City.

Among 85 percent of participants who had previously undergone HIV testing, 43 percent reported rapid testing at their most recent test. In terms of future testing, 64 percent would seek rapid testing vs. 36 percent who would seek traditional testing. MSM who preferred rapid testing were significantly more likely to have attended at least some college, to have discussed HIV testing with a sexual partner, to be aware of rapid testing, and to have had a prior HIV test.

“In general, young MSM of color seem aware of rapid testing. However, our results indicate the need to carefully consider the unique needs of those who are particularly disenfranchised or engaged in high-risk behaviors and who may need concerted efforts around HIV counseling and testing,” the authors concluded. “Likewise, our findings point to a need for more effective education and social marketing strategies.”

**Neonatal Circumcision Yet to Gain Ground**

*Inter Press Service, (09.30.2010) Ignatius Banda*

The Ministry of Health and Child Welfare this year began promoting neonatal male circumcision, which is seen as a way to lower HIV infection rates in the long term. But as is the case with adult male circumcision, uptake of neonatal male circumcision is slow. Studies show male circumcision reduces the risk of female-to-male HIV transmission by up to 60 percent.

According to the ministry, just 5,000 Zimbabwean men have been circumcised since 2007. New mothers are reluctant to circumcise their infants, reports midwife Thubelihle Mkhwebu. Many new mothers have said the HIV fight should be confined to adults and do not want their babies “cut up.” “We still have a lot of convincing to do,” she said.

Cultural activists say male circumcision is a dying tradition in Zimbabwe, though some communities still perform the procedure as part of a rite of passage. “Not many new mothers quite understand why an infant has to be circumcised and many claim this is not part of their culture and even their religion,” said Mkhwebu.

The ministry’s goal is to have 80 percent of newborn males and sexually active adult males circumcised by 2015.

The slow uptake of neonatal male circumcision thus far also might be attributed to a continuing lack of comprehensive knowledge and understanding about HIV/AIDS among many Zimbabweans, as noted in the country’s 2009 Multiple Indicator Monitoring Survey. It found that HIV/AIDS knowledge tends to increase with education and wealth. The reluctance to have male babies circumcised comes largely from mothers attending clinics in poor working-class suburbs, and there are concerns it could take some time for attitudes to change.

**Failing to Control Tuberculosis**

*Inter Press Service, (09.29.2010) Wambi Michael*

Uganda is struggling to get TB under control, experts say. Many patients lack an understanding of the disease, have difficulty in reaching clinics for follow-up appointments, and face drug shortages. The nation is among the 22 countries with the highest TB burden, according to the World Health Organization (WHO).

The government declared TB to be an emergency in 2005, and it allocated 38 percent of the health department’s budget to fight the disease. Of TB patients in Uganda, 16 percent fail to adhere to treatment, the health department says. Just over half of all TB cases are diagnosed, far less than WHO’s 75 percent target, and treatment success is achieved by 68 percent, well short of WHO’s 85 percent goal.
The government has put its energy behind increasing the number of clinics in order to improve TB diagnosis and treatment. However, resources are short for drug procurement and community education campaigns. In such campaigns, informational sessions are used to teach the public how TB is prevented, detected, and treated.

“Community and family members can help identify TB and encourage anyone who has a cough for more than two weeks to go for screening,” said Dr. Francis Adatu, national TB and leprosy manager. Educating the community can help by promoting early detection to limit TB’s spread.

Outside donors fund 95 percent of the cost of TB drugs in Uganda, with the major supporters being the Global Fund to Fight AIDS, TB and Malaria and the US President’s Emergency Plan for AIDS Relief. James Kakooza, minister for primary health care, said support has ebbed since 2008, and the government is seeking additional support from those donors.


American Journal of Public Health Vol. 100; No. 9: P. 1724-1729, (09..2010)   Heather J. Menzies, MD, MPH; Carla A. Winston, PhD, MA; Timothy H. Holtz, MD, MPH; Kevin P. Cain, MD; William R. MacKenzie, MD

In the current study, researchers with CDC’s Division of Tuberculosis Elimination examined TB cases and case rates among US- and foreign-born children and adolescents (C&A). They also analyzed the potential effect of changes to overseas TB screening for immigration applicants.

Based on case data from the National Tuberculosis Surveillance System from 1994 to 2007, the study found foreign-born C&A accounted for 31 percent of the 18,659 reported TB diagnoses in persons younger than 18. During the study period, TB rates declined 44 percent among foreign-born C&A (20.3 per 100,000 to 11.4 per 100,000) and 48 percent among US-born C&A (2.1 per 100,000 to 1.1 per 100,000).

TB rates were nearly 20 times higher among foreign-born than US-born C&A. Of foreign-born patients with known month of US entry (88 percent), more than 20 percent were diagnosed with TB within three months of entry.

“Marked disparities in TB morbidity persist between foreign- and US-born children and adolescents,” the study authors concluded. “These disparities and the high proportion of TB cases diagnosed shortly after US entry suggest a need for enhanced pre- and post-immigration screening.”

Symptoms still common in patients with HIV, and associated with poor adherence and risky sex

Michael Carter
Published: 06 October 2010

Physical and psychological symptoms are highly prevalent in HIV-positive patients, investigators from the UK report in the online edition of Sexually Transmitted Infections.

Unprotected sex with a partner of an unknown or different HIV status and poor adherence to HIV treatment were both associated with a high burden of psychological symptoms.

“The patient burden of disease remains high, and outcomes are unlikely to be improved without careful attention to the patient experience of disease and a clinical focus beyond virology”, comment the investigators.

From the time of seroconversion, HIV infection is associated with a high prevalence of distressing symptoms. The World Health Organization recommends that interventions to control pain and symptoms should be an essential part of HIV care.

However, research suggests that physicians often fail to detect symptoms in their patients, and that many individuals with HIV are living with untreated pain and other symptoms.

Investigators in London and south-east England were concerned about this lack of attention to symptoms. They also wished to see how prevalent symptoms were in their patients and if experiencing symptoms was associated with adherence to HIV treatment, unprotected sex, and disclosure of HIV status to sex partners.

Therefore, in 2005-06 a total of 778 patients took part in a cross-sectional study.

Study participants were asked to provide demographic information and to say if they had experienced any of 26 physical or psychological symptoms in the past seven days. The distress caused by symptoms was scored on a scale of 0-4.
Information was also sought on the use of antiretroviral therapy. Those taking HIV treatment were asked to report their level of adherence in the previous week. All individuals were asked if they had had unprotected sex with a partner who was HIV-negative or of unknown status in the previous three months and if they disclosed their HIV status to partners.

Most (66%) of the participants were gay or bisexual men and were white (67%). The mean age was 40 years. A little over half (51%) of patients were born in the UK, and 45% had a degree.

Over two-thirds (67%) of patients were taking HIV therapy. Complete adherence to treatment was reported by 42%; partial adherence by 36%; and poor adherence by 22%. A third of patients taking treatment had switched therapy once and 40% reported multiple treatment changes.

A total of 11% of patients reported unprotected sex in the previous three months with a partner who may have been HIV-negative, and 6% had never disclosed to a sex partner.

Symptoms were highly prevalent. The mean number of reported symptoms was 18. The mean symptom physical distress score was 0.81, the mean psychological distress score was 1.34, and the global distress score was 1.16.

Lack of energy was reported by 71% of patients, tiredness by 68%, difficulty sleeping by 62%, poor concentration by 61%, worry by 70%, sadness by 66%, diarrhoea by 54% and sexual problems by 53%.

Possession of a degree was associated with less symptom-related physical (p = 0.007), emotional (p = 0.004), and overall (p = 0.021) distress.

In addition, white patients reported less symptom related distress (p = 0.04) than those of other ethnicities. The investigators think that this could be because many black African patients in the UK are diagnosed late when they are ill because of HIV and therefore likely to be experiencing symptoms.

Disclosure of HIV was significantly associated with fewer symptoms (p = 0.021), and reporting unprotected sex with a partner who may have been HIV-negative was associated with a greater number of psychological symptoms (p = 0.047).

"Interestingly", write the investigators, "currently being on antiretroviral therapy was not significantly associated with any of the symptom measures."

Analysis was then restricted to the patients who were taking HIV treatment. Poor adherence was significantly associated with psychological (p = 0.001) and global distress (p = 0.006). Switching treatment was associated with both physical (p = 0.003) and psychological distress (p = 0.006) caused by symptoms, as well as a greater number of total symptoms (p = 0.013).

Being born in the UK and having a degree were both associated with a lower burden of physical symptoms.

"The data...reveal high 7-day prevalence and associated distress of burdensome symptoms", comment the investigators, who conclude: “It is essential that quality management of HIV disease routinely assess these distressing problems, so that key outcomes of risk behaviour and adherence may be optimally influenced.”

Reference
Harding R et al. Symptoms are highly prevalent among HIV outpatients and associated with poor adherence and unprotected sexual intercourse. Sex Transm Infect, online edition, 2010 (click here for access to free abstract and paid-for full text).

Immune system linked with accumulation of toxic tau protein

Cells that help to protect the central nervous system may also contribute to pathological changes in the brain. New research, published by Cell Press in the October 7th issue of the journal Neuron, provides mechanistic insight into a link between the immune system and neurodegenerative disorders like Alzheimer's disease that are associated with abnormal accumulation of tau protein.

Tau is a protein found inside of neurons that acts almost like a skeleton, providing a supportive framework for the cell. However, abnormal tau sometimes clumps into filamentous deposits that damage neurons. It is well established that aggregates of microtubule associated protein tau (MAPT) with multiple phosphate groups attached are a defining feature of neurodegenerative disorders called "tauopathies", which include some movement disorders along with Alzheimer's disease and other dementias.

Tauopathies are increasingly common neurodegenerative diseases with over 5 million people in the US with AD and millions more affected by non-AD tauopathies. Previous research suggested a link between inflammation in the nervous system and the tauopathies. More specifically, cells called microglia which play a key role in the immunity of the nervous system have been implicated in the pathogenesis of multiple neurodegenerative disorders. "While some research has suggested a correlative link between neuroinflammation and tauopathies, there is little mechanistic evidence that altered microglial activation plays a pathogenic role in the formation of MAPT pathologies,"

Reference
Harding R et al. Symptoms are highly prevalent among HIV outpatients and associated with poor adherence and unprotected sexual intercourse. Sex Transm Infect, online edition, 2010 (click here for access to free abstract and paid-for full text).
explains senior study author, Dr. Bruce T. Lamb from the Department of Neurosciences at the Cleveland Clinic.

In order to examine the link between microglia and tauopathy, Dr. Lamb and colleagues studied a specific signaling pathway through which neurons and microglia communicate, fractalkine (CX3CL1), a chemokine expressed in neurons, and its receptor (CX3CR1) which is expressed exclusively in microglia. Dr. Lamb's group evaluated perturbations of this signaling pathway in several different model systems, including a mouse model of inflammation, a mouse model of tauopathy (hTau) and microglia and neurons grown in the laboratory. They found that microglial inflammation promoted MAPT phosphorylation and aggregation in all of the model systems.

"Importantly, introduction of CX3CR1 deficiency into hTau mice resulted in altered microglial activation, enhanced MAPT phosphorylation and aggregation, as well as behavioral abnormalities," says Dr. Lamb. In addition to documenting the effects of a specific microglial receptor on MAPT pathology, the researchers also gained new insight into specific signaling molecules downstream of the CX3CL1/CX3CR1 interaction. Taken together, the findings reveal a direct link between the activation of microglia and the abnormal phosphorylation and aggregation of MAPT in neurons and suggest potential novel therapeutic strategies for tauopathies.

One lock, many keys
In order to track down pathogens and render them harmless, the immune system must be able to recognize myriad different foreign substances and react to them. Scientists at the Max Planck Institute of Immunobiology and the Centre for Biological Signalling Studies BIOSS at the University of Freiburg have discovered how the immune system's B-cells can be activated by numerous substances from our environment. The receptor molecules on the surface of the B-cells are only activated when the receptor subunits separate following the binding of foreign substances. These findings turn the previous understanding of how B-cell receptors are activated on its head and may contribute to the development of new vaccination strategies and treatments for B-cell tumours. (*Nature*, September 23, 2010)

Many human diseases, like the increasing number of autoimmune diseases and B-cell tumours such as leukaemia and lymphoma, are triggered by overactive receptors on the surface of white blood cells known as B-lymphocytes or B-cells. Each B-cell has up to 120,000 B-cell receptors on its surface. The activation of these receptors causes the cell to form antibodies. The receptors work on the basis of the lock and key principle, whereby a receptor (the lock) can only be activated by a matching substance (key) and trigger an immune response. If millions of keys can open one lock, the question arises as to how this lock works and how we are protected against the continuing over-activity of our immune response.

Jianying Yang und Michael Reth have now found an answer to this mystery of immune system activation. Using methods from synthetic biology they recreated the mouse B-cell receptor in a fruit-fly cell. Unlike in the previous research carried out in this area, the focus of their attention was the receptor on resting B-cells, the non-activated cells. To their surprise they discovered that the receptor on resting B-cells consists of several different sub-units and forms oligomers. In this form, sectors of the receptors that play an important role in signal transmission are concealed. If a matching binding partner bonds to the receptor, the oligomers disintegrate and the individual sub-units can become active. "The separation process is largely dependent on the structure of the binding partner. This explains why the B-cell receptor can be activated by thousands of different substances," explains Michael Reth from the Max Planck Institute of Immunobiology. The discovery that the sub-units of the B-cell receptors form ordered oligomer complexes also leads to the conclusion that the receptors on resting B-cells can only be activated under precisely defined conditions.

Accepted doctrine refuted
The new model for the activation of the receptor is at variance with the hitherto accepted scientific doctrine. Up to now it was believed that the receptors exist in an unordered form in the cell membrane and only aggregate when they make contact with a binding partner. "In contrast, our new model is based on the dissolution and not the formation of a particular receptor structure. This marks a turning point in immunology research and, possibly also, in the field of cell biology," stresses Michael Reth. It appears that
other receptor molecules also form oligomers in a resting state which only become active when they disintegrate into subunits or change their conformation.


New Sex Education Funding Ends Decade of Abstinence-Only
Associated Press, (10.01.2010) Kelli Kennedy
As part of its new five-year, $375 million Health and Human Services (HHS) grant, the federal government, for the first time in more than a decade, is funding sex education programs that go beyond the abstinence-only approach.

Beginning this year, the grants are being divided among 28 programs that have been proven to demonstrate lower pregnancy rates among participants, following evaluations by the independent Mathematica Policy Research. To qualify, programs had to be supported by at least one study showing a positive, statistically significant effect on one of the following: sexual activity, contraceptive use, STDs, pregnancy or births.

Many HHS programs distribute condoms, but about half take an “above the waist” approach—giving kids the tools they need to help them succeed in school and make better life decisions, particularly about sex.

“There's a growing realization that we have to talk to young people about relationships. It’s not just body parts,” said Bill Albert, chief program officer for the National Campaign to Prevent Teen and Unplanned Pregnancy. “It’s saying, ‘What are your goals?’ and helping young people understand what they need to do to get there.”

Abstinence programs will continue to receive $50 million annually through a federal grant that requires states to match $3 for every $4; so far, about 30 states have applied for that money. The new HHS programs do not require states to provide matching funds.

Less than 15 percent of the nine-month, HHS-approved Teen Outreach Program curriculum is spent addressing sex education, despite that being its chief goal. TOP encourages teens to identify a need in their community and spend at least 20 hours working on it, developing problem-solving and leadership skills. Participants have a 53 percent lower risk of pregnancy and a 60 percent lower risk of school course failure.

HIV a Threat to Those Age 50 and Older
Older New Yorkers should take precautions to prevent HIV infection, Dr. Richard F. Daines, the state commissioner of health, warned recently. The number of state residents over age 50 with HIV is rising, partly because antiretroviral therapy has helped increase their life expectancy. Many others, however, are newly infected or diagnosed late in the course of the disease, according to data from the State Department of Health’s AIDS Institute.

“There is a misperception among some people that persons age 50 and older don’t get infected with HIV—that it is something that just younger people need to worry about,” Daines said. “But the data in New York state clearly show that being 50 or 60 years of age doesn’t protect you from acquiring this disease.”

New Yorkers in the 50-plus set account for more than 47,000 people living with HIV/AIDS in the state. In 2008, they represented 38 percent of all state HIV/AIDS cases, up from 23 percent five years earlier.

Among the state’s reported HIV diagnoses in 2008, 764 were in people age 50 and older. Nearly half progressed to AIDS within a year of HIV diagnosis, meaning they were tested late, probably years after acquiring HIV, said Daines.

To address the often unrecognized threat of HIV infections among older adults, the AIDS Institute recently held a forum, titled “Red Ribbon, Silver Threads: Healthy Aging in the Era of HIV/AIDS.” To see a report from the proceedings, which attracted more than 170 experts in geriatrics, chronic disease, and HIV/AIDS, visit: http://www.health.state.ny.us/diseases/aids/conferences/index.htm.
Modelling study: no condom use after recent viral load test safer than intermittent condom use
Roger Pebody
Published: 07 October 2010
In stable gay couples, where one partner is taking HIV treatment and the other is HIV-negative, the risk of HIV transmission is relatively low if condoms are not used following a recent undetectable viral load test result. However, using condoms on a few more occasions but without reference to viral load substantially increases the risk of HIV transmission. These are the findings of a mathematical modelling study, drawing on detailed data on viral loads in Dutch gay men, published online ahead of print in Sexually Transmitted Infections.

The model suggests that during the entire period that a first-line treatment regimen is taken, the risk of HIV transmission would be 1% if condoms are used all the time, 3% if condoms are not used after an undetectable viral load test in the past six months, 17% if condoms are used 30% of the time, and 22% if condoms are never used.

Using condoms is most crucial when patients have not recently (within the past 3 months) had an undetectable viral load measurement.

The model was designed to test the proposition put forward in the Swiss statement: that in long-term, serodiscordant couples, a decision to give up using condoms can be safely made as long as the HIV-positive partner is adhering to HIV treatment and has had an undetectable viral load for at least six months.

However it is important to note that the model does not take into account the increased risk of HIV transmission when one of the partners has a sexually transmitted infection. The Swiss statement emphasised that unprotected sex could only be safe if neither partner had a sexually transmitted infection.

This is not the first modelling study conducted to explore the prevention impact of HIV treatment in Western countries (for example others have been conducted by researchers in Canada and Australia). However it is the first to take into account the factor that deciding not to use condoms might be conditional on the most recent viral load measurement being undetectable.

Researchers from Imperial College London and the HIV Monitoring Foundation in Amsterdam developed a stochastic mathematical stimulation model of viral load trends, frequency of viral load testing and HIV transmission risk, drawing on data from a cohort of HIV-positive people in the Netherlands.

The model looked at transmission risk within a stable relationship between two men of different HIV statuses, where the relationship continued for the duration of the first-line HIV treatment regimen.

The researchers based their assumptions about the relationship between viral load and infectiousness on previous modelling work, adjusted to take into account the increased risk of HIV transmission during anal sex rather than vaginal sex.

They also assumed that each couple has anal sex 100 times a year and that condoms reduce transmission risk by 95% (but not more, because they may break or be used incorrectly).

In order to account for a range of other plausible scenarios (for example, less frequent sex in the relationship or a higher transmission risk), the researchers conducted a series of alternative analyses. The results of these are presented as a combined 95% uncertainty interval: the lower and upper figures represent a range of plausible results.

The estimated risk of transmission during first-line therapy is as follows:

- If condoms are always used: 1% (uncertainty interval: 0%–7%).
- If condoms are always used unless the most recent viral load result, taken in the past six months, is undetectable: 3% (uncertainty interval: 0.2%–8%).
- If condoms are used 30% of the time: 17% (uncertainty interval: 7%–29%).
- If condoms are never used: 22% (uncertainty interval: 9%–37%).

The researchers note that the results for using condoms for 30% of sex acts are broadly similar to those of men never using them. Men following the viral load strategy would in fact use condoms on fewer occasions (10% of the time), but their risk of transmitting HIV would be substantially lower.

An additional analysis of alternative viral load strategies showed that only giving up condoms if an undetectable viral load had been recorded in the past three months would further reduce the transmission risk, whereas making the decision based on the most recent viral load test result (even if it was more than six months ago) would increase the risk of transmission.
These results lead the researchers to emphasise the importance of more frequent viral load monitoring and of minimising losses to follow-up. “Without such effort, increases in viral load go undetected, exposing partners to higher risks of transmission.”

They say that their results show that “basing the decision to use condoms on viral load provides substantially more protection to partners than incomplete condom use, provided that the measurement is within the past 3-6 months.”

The researchers conclude: “The implications of this work are that the key message to patients should remain that always using condoms when receiving treatment is the best way to protect partners from the risk of HIV transmission. However, an additional message is that using condoms is most crucial when patients have not recently (within the past 3 months) had an undetectable viral load measurement.”

Reference

HIV infections could hit 3.2m a year by 2031 if funding is not increased
Just keeping pandemic under control will cost up to $733bn, report published in the Lancet warns

Merely controlling HIV and AIDS will cost between $397bn and $733bn over the next 20 years – and unless more money is spent the pandemic will continue to spread, experts warned today.

If funding is not increased from 2009, infections could rise from 2.3 million a year to 3.2 million by 2031, claimed a report by the aids2031 financing group, headed by the Results for Development Institute in Washington DC.

In the Lancet medical journal, the group warns it is “increasingly improbable” in tough economic times that donors and governments will find enough money to fund a rapid increase in universal access to prevention and treatment services by 2015. It is estimated that would prevent about 7 million more deaths and 14.2 million infections than if efforts continued on the present scale.

Just this week, donors in New York pledged $11.7bn for the Global Fund to fight AIDS, TB and malaria, less than the $13bn it had set as the minimum to fund the current disease-fighting programmes. The Global Fund and PEPFAR (the US president’s emergency plan for Aids relief) are the two biggest sources of funding for Aids prevention and treatment in developing countries.

However, the aids2031 paper did reveal more efficient ways of using the funding available. And some developing countries with higher incomes and less intense epidemics, such as China, India and the Ukraine, may be capable of taking over the costs of fighting HIV themselves, leaving more money for poorer countries.

The figures, said Dr Robert Hecht, the managing director of the institute and lead author of the paper, “suggest that we have a long, hard road ahead of us in terms of what it is going to take to combat AIDS. But there is a window of opportunity in the next couple of years. Countries can really change where they are going in terms of how many lives they save and infections they prevent.

“It is a hopeful message. The leaders in these countries have some rather distinct choices. The key thing is to spend the money extremely well and get the most value from it.”

That would include investing in effective prevention techniques, such as circumcision, while mounting behaviour change campaigns and seeking low-cost drugs for treatment.

The authors identify three distinct groups of countries – those with high burden of disease and low income (such as Mozambique), those with low disease burden and middle income (such as China) and those with high disease burden and middle income (such as South Africa).

The situation in the poorest, such as Zambia, Mozambique, Kenya, Malawi and Uganda, is most worrying and unlikely to improve in the next few years. “What these countries are starting to spend is going to be anywhere between 3% and 6% of GDP. That is a staggering fact to think about.”

The group warns that even if the world adopted the most comprehensive strategy currently possible for preventing transmission of the disease, HIV would not be halted. They estimate that 1.2 million people would still become infected in 2031, “meaning that even under the best circumstances there will be a persisting epidemic in 2031, 50 years after the emergence of HIV/AIDS.” Without a technological breakthrough such as a vaccine, HIV will continue to spread.
Study Sheds Light on How HIV Evades Immune Response

SUMMARY: Study findings from researchers at New York University published in the September 9, 2010 issue of Nature help explain how dendritic cells—which facilitate HIV infection of CD4 T-cells—manage to avoid becoming productively infected themselves. HIV can enter these cells, but does not integrate its genetic material into the host cell genome. If this protective mechanism can be harnessed, it could potentially aid development of an HIV vaccine to protect CD4 cells.

Below is the text of a press release from NYU Langone Medical Center describing the research and its findings.

Novel Sensing Mechanism Discovered in Dendritic Cells to Increase Immune Response to HIV

Finding by NYU Langone Researchers Could Lead to Vaccine Development

September 08, 2010—Dendritic cells are the grand sentinels of the immune system, standing guard 24/7 to detect foreign invaders such as viruses and bacteria, and bring news of the invasion to other immune cells to marshal an attack. These sentinels, however, nearly always fail to respond adequately to HIV, the virus causing AIDS. Now a team of scientists at NYU Langone Medical Center has discovered a sensor in dendritic cells that recognizes HIV, spurring a more potent immune response by the sentinels to the virus. They report their findings in the September 9, 2010, issue of Nature.

"This is the first time that an alarm system that recognizes retroviruses like HIV has been discovered," says Dan Littman, MD, PhD, the Helen L. and Martin S. Kimmel Professor of Molecular Immunology in the Departments of Pathology and Microbiology at NYU Langone Medical Center and a Howard Hughes Medical Institute investigator, and the study's lead author.

"The ability to stimulate a protective immune response against HIV is critical to the development of therapeutic or preventive vaccines for the virus," says Dr. Littman. In contrast to normal vaccines, which prevent infection, therapeutic vaccines are designed to boost the severely weakened immune systems of people infected with HIV.

Dendritic cells, named for their branching, tree-like shape, have been called the maestros of the immune system because they orchestrate a dynamic range of immune responses. These cells have attracted intense interest from researchers in many fields because of their potential to fight disease and prevent rejection of organ transplants.

When a dendritic cell captures a dangerous pathogen, it tears it apart and delivers a piece to the soldiers of the immune system cells, called T-cells, which in turn expand like a clonal army to coordinate immune defenses and destroy the invader. But dendritic cells fail to recognize HIV as a danger. Instead, HIV exploits the cells to get a free ride to T-cells, which become infected with the virus. "The virus actually infects the same soldiers that are supposed to protect us from it," explains co-author Derya Unutmaz, MD, associate professor in the Departments of Microbiology, Pathology and Medicine at NYU Langone Medical Center.

Although HIV enters dendritic cells, an unknown mechanism blocks the virus from infecting them—going into the nucleus of the cells to make copies of itself. Recently, a technique was discovered to overcome this block by bathing the cells with a protein derived from SIV, a relative of HIV that only infects monkeys. Using these techniques, the researchers discovered that when HIV was forced to enter the nucleus of dendritic cells, the cells unexpectedly recognized the virus as an intruder and went into action to initiate a program to stimulate a stronger T-cell response against the virus.

What set off the alarm, the researchers found, was a protein called capsid, which encapsulates HIV’s genetic material. "It’s surprisingly unexpected that the sensing mechanism of the dendritic cell recognizes the capsid of the virus, rather than the genetic material inside," says co-author Nicolas Manel, PhD, of the Kimmel Center for Biology and Medicine at the Skirball Institute at NYU Langone Medical Center and the Institut de Genetique Moleculaire de Montpellier. "Nevertheless, by adding elements of this capsid to a vaccine," says Dr. Manel, "it may be possible to improve the immune response of those who already have HIV or actually mount a potent immune response before the individual is infected."

"We still don’t understand why this sensor is triggered only when we force HIV to integrate into dendritic cell genome to make its own copies," adds Dr. Unutmaz. "One possibility is that this cryptic sensing mechanism has evolved to recognize the thousands of ancient retroviruses that have infected us in the past and now make up almost 10% our genome. It is conceivable that dendritic cells have evolved this internal sensor in case any of these archaic retroviruses were reawakened. Nonetheless, the finding is extremely exciting because not only it could lead to new directions in HIV vaccine research but it can also be exploited to enhance vaccines against other viruses." 10/5/10
Bridging the Gap: Using School-Based Health Services to Improve Chlamydia Screening Among Young Women

American Journal of Public Health Vol. 100; No. 9: P. 1624-1629, (09..2010) Rebecca A. Braun, MPH; Jackie M. Provost, MPH

The study’s objective was to implement a chlamydia screening program targeting young women accessing reproductive health care services in a school-based setting, and to assess racial/ethnic factors associated with infection.

From January 2008 to December 2008, the California Family Health Council partnered with nine health care agencies receiving federal Title X family planning funding and 19 educational institutions to implement the Educational Partnerships to Increase Chlamydia Screening (EPICS) program.

A total of 3,396 unique sexually active females received reproductive health care at EPICS agencies, of whom 85 percent self-reported no other source for reproductive health care. Chlamydia testing was given to 3,026 clients (89.1 percent chlamydia screening coverage); 5.6 percent of those screened tested positive for the infection. Clients who were African-American (odds ratio [OR]=7.5; 95 percent confidence interval [CI]=3.9, 14.3), Pacific Islander (OR=4.1; 95 percent CI=1.1, 15.5) or Asian (OR=3.3; 95 percent CI=1.4, 8.1) were more likely to test positive for chlamydia than were white clients.

“Chlamydia screening programs implemented in school-based settings have the capacity to identify and treat a significant amount of asymptomatic infection in a population that otherwise may not be reached,” the authors concluded. “To facilitate screening, school-based clinics should implement outreach strategies that target their school population and clinical strategies that maximize opportunities for screening.”

Studying Illnesses Caused by Worms

Scientist Are Learning How Immune Cells Communicate

Saranac Lake, N.Y. – A billion people living in underdeveloped areas around the world are infected with parasitic helminthes, worms that survive by residing in and feeding on their hosts. These infestations can cause chronic intestinal (and occasionally systemic) illnesses leading to long-term disability. Irah King and Markus Mohrs, biomedical researchers at the Trudeau Institute, are investigating illnesses caused by these gut-dwelling worms in an effort to decipher how immune cells send and receive signals that determine the specific immune response to mount.

In a study reported in the current issue of the Journal of Immunology, Dr. King and his colleagues demonstrate that a soluble factor released by CD4+ T cells (a subset of cells that aid B cells in generating an immune response) called interleukin-21 (IL-21) instructs B cells to produce antibodies that bind helminth-derived products and inhibit their ability to mature into adult worms in the host.

Using genetically modified mice that lack the receptor for IL-21, they found that B cells directly require IL-21 signals in order to differentiate into plasma cells, the major antibody-producing B cell subset. The role of IL-21 signaling in this context seems to be specific because it does not impact other forms of B cell activation or CD4+ T cell differentiation, another leukocyte subset critical for protective immunity to helminthes.

“It is already established that B cells must produce antibodies to protect us from gut-dwelling worms and other parasitic infections,” said Dr. King. “However, the signals that B cells need to receive in order to produce antibodies following infection are not yet completely understood.”

Scientists who study anti-parasite immunity understand that immune responses generated by worm infections are in many ways similar to responses generated by diseases more common in the developed world like asthma, allergies, and ulcerative colitis. By identifying these similarities, Dr. King and other researchers hope to point to new treatments and therapies for a host of diseases associated with problems in immune system regulation.
Yersinia Pestis Bacteria Confirmed as Cause of Middle Ages 'Black Death' Plague Epidemic

ScienceDaily (Oct. 8, 2010) — The latest tests conducted by anthropologists at the Johannes Gutenberg University Mainz (JGU) have proven that the bacteria Yersinia pestis was indeed the causative agent behind the "Black Death" that raged across Europe in the Middle Ages.

The cause of the epidemic has always remained highly controversial and other pathogens were often named as possible causes, in particular for the northern European regions. Using DNA and protein analyses from skeletons of plague victims, an international team led by the scientists from Mainz has now conclusively shown that Yersinia pestis was responsible for the Black Death in the 14th century and the subsequent epidemics that continued to erupt throughout the European continent for the next 400 years. The tests conducted on genetic material from mass graves in five countries also identified at least two previously unknown types of Yersinia pestis that occurred as pathogens.

"Our findings indicate that the plague traveled to Europe over at least two channels, which then went their own individual ways," explains Dr Barbara Bramanti from the Institute of Anthropology of Mainz University. The works, published in the open access journal PLoS Pathogens, now provide the necessary basis for conducting a detailed historical reconstruction of how this illness spread.

For a number of years, Barbara Bramanti has been researching major epidemics that were rampant throughout Europe and their possible selective consequences as part of a project funded by the German Research Foundation (DFG). For the recently published work, 76 human skeletons were examined from suspected mass graves for plague victims in England, France, Germany, Italy, and the Netherlands. While other infections such as leprosy can be easily identified long after death by the deformed bones, the problem faced in the search for plague victims lies in the fact that the illness can lead to death within just a few days and leaves no visible traces.

With luck, DNA of the pathogen may still be present for many years in the dental pulp or traces of proteins in the bones. Even then it is difficult to detect, and may be distorted through possible contamination. The team led by Bramanti found their results by analyzing old genetic material, also known as ancient DNA (aDNA): Ten specimens from France, England, and the Netherlands showed a Yersinia pestis-specific gene. Because the samples from Parma, Italy and Augsburg, Germany gave no results, they were subjected to another method known as immunochromatography (similar to the method used in home pregnancy tests for example), this time with success.

Once the infection with Yersinia pestis had been conclusively proven, Stephanie Hänsch and Barbara Bramanti used an analysis of around 20 markers to test if one of the known bacteria types "orientalis" or "medievalis" was present. But neither of these two types was found. Instead, two unknown forms were identified, which are older and differ from the modern pathogens found in Africa, America, the Middle East, and the former Soviet Union regions. One of these two types, which are thought to have contributed significantly to the catastrophic course of the plague in the 14th century, most probably no longer exists today. The other appears to have similarities with types that were recently isolated in Asia.

In their reconstruction, Hänsch and Bramanti show an infection path that runs from the initial transportation of the pathogen from Asia to Marseille in November 1347, through western France to northern France and over to England. Because a different type of Yersinia pestis was found in Bergen op Zoom in the Netherlands, the two scientists believe that the South of the Netherlands was not directly infected from England or France, but rather from the North. This would indicate another infection route, which ran from Norway via Friesland and down to the Netherlands. Further investigations are required to uncover the complete route of the epidemic.
"The history of this pandemic," stated Hänsch, "is much more complicated than we had previously thought."

**Journal Reference:**

**Bacteria Can Stand-Up and ‘Walk’**

ScienceDaily (Oct. 8, 2010) — Many drug-resistant infections are the result of bacterial biofilms, structured aggregates of bacteria that live on surfaces and that are extremely resistant to environmental stresses. These biofilms impact human health in many ways—cystic fibrosis, for example, is a disease in which patients die from airway bacterial biofilm infections that are invulnerable to even the most potent antibiotics.

Now, UCLA researchers and their colleagues have found that during the initial stages of biofilm formation, bacteria can actually stand upright and “walk” as part of their adaptation to a surface.

“Bacteria exist in two physiological states: the free-swimming, single-celled planktonic state and the surface-mounted biofilm state, a dense, structured, community of cells governed by their own sociology,” said Gerard Wong, a professor of bioengineering at the UCLA Henry Samueli School of Engineering and Applied Science and at the California NanoSystems Institute at UCLA.

“Bacteria in biofilms are phenotypically different from free-swimming bacteria even though they are genomically identical. As part of their adaptation to a surface and to the existence of a community, different genes are turned up and down for bacteria in biofilms, leading to drastically different behavior,” he said.

In the study, which appears in the current issue of the journal Science, Wong and his research group describe the new surface adaptation—the “walking” motility mechanism, which was observed in *Pseudomonas aeruginosa*, a biofilm-forming pathogen partly responsible for the lethal infections in cystic fibrosis.

What enables this upright walking are appendages called type IV pili, which function as the analog of legs. What’s more, walking allows *P. aeruginosa* to move with trajectories optimized for surface exploration, so that they can forage more effectively. The upright orientation is also the first step in surface detachment for bacteria.

“We’ve shown that vertical orientation plays a critical role in key life-cycle events: vertically oriented bacteria can more readily detach from surfaces, allowing them to spread and disperse effectively,” said Jacinta Conrad, a former postdoctoral researcher with Wong’s group and an assistant professor of chemical and biomolecular engineering at the University of Houston. "Our unique contribution is to directly relate single-cell behavior to specific events in the bacterial life cycle and thereby show how single-cell motility influences biofilm morphology."

The research team was able to develop a series of search engines and computer programs that use particle-tracking algorithms to quantitatively analyze time-lapse microscopy movies of bacterial motion on surfaces.

“Previously, graduate students had to look at cells manually and then laboriously track them from one frame to the next,” Wong said. "Our computational approach allows us to increase the volume of data analyzed 100,000-fold and to perform the necessary analysis in a few hours rather than a few months. Moreover, we make sense of this mountain of information using search engine-based approaches. This represents a big advance in the way microscopes are used."

The work was conducted in collaboration with a research group at the University of Notre Dame led by Joshua Shront, an assistant professor in the department of civil engineering and geological sciences and at the Eck Institute for Global Health.

"*P. aeruginosa* infections are unfortunately the leading cause of death for individuals with cystic fibrosis," Shront said. "In addition to these lung infections, *P. aeruginosa* also causes skin, eye and gastrointestinal infections. As we learn how *P. aeruginosa* colonizes surfaces, perhaps we can develop better methods to treat these infections."

"One of the most exciting factors of this work for me is the potential for widespread impact,” Conrad said. "Biofilm formation is ubiquitous in human health and also in a variety of industrial settings. Biofouling due to biofilm formation increases the hydrodynamic drag on ships, leading to increased fuel consumption, and also contributes to increased costs in water treatment, oil recovery and food processing."

21
Controlling biofilm formation will therefore allow us to reduce biofouling-related problems across a wide range of industries."

**Journal Reference:**

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**Melanoma Uses Body's Immune System to Spread to Lungs**

*ScienceDaily* (Oct. 8, 2010) — The way melanoma cells use the immune system to spread and develop into lung tumors may lead to a therapy to decrease development of these tumors, according to Penn State researchers.

"Melanoma is the most aggressive and metastatic form of skin cancer,” said Gavin Robertson, professor of pharmacology, pathology, dermatology and surgery in the Penn State College of Medicine. "Therefore, identifying proteins and molecular mechanisms that regulate metastasis is important for developing drugs to treat this disease.”

Metastasis is a complex process in which cancer cells detach from the primary tumor and migrate to other sites in the body by traveling through the lymphatic or blood circulatory systems. Researchers in the Foreman Foundation Melanoma Research Laboratory at Penn State developed a model to determine why the roughly one million tumor cells shed daily from a 1-gram melanoma tumor do not form more metastases in the lungs.

After intravenously injecting 1 million human melanoma cells in a mouse, Robertson and colleagues observed entrapment of many of these cells in the lung vessels. Within 24 hours, however, few cells were still present in the lungs.

"In this study, we show that entrapped, circulating melanoma cells can use a person's own immune cells—specifically a type of white blood cell called neutrophils—to control lung metastasis development,” Robertson said. After injecting the mice with neutrophils an hour following the melanoma cell injection, cancer cell retention was increased in the lung by about three times.

Melanoma cells produce and secrete high levels of a protein called IL-8, which is used to attract neutrophils.

"For patients, this is important because a therapy preventing circulating melanoma cells from secreting IL-8 would have the potential to decrease lung metastasis development by about 50 percent by disrupting interaction of the cancer cells with neutrophils,” Robertson said. "Metastases form by proteins on the melanoma and neutrophils interacting and forming physical connections. These connections promote anchoring of the melanoma cells to the lung vessel walls, enabling the cancer cells to migrate through the wall to form lung metastases.”

Decreasing the secretion of IL-8 limits the interaction of melanoma cells with neutrophils, dropping the number of melanoma cells retained in the lungs by about half.

Findings were published in the journal *Cancer Research*. Funding for the study was provided by the National Institutes of Health and the Foreman Foundation for Melanoma Research.

**Journal Reference:**

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**How Bacteria Become Resistant to Antibiotics**

*ScienceDaily* (Oct. 8, 2010) — A study by two Florida State University biochemists makes an important contribution to science’s understanding of a serious problem causing concern worldwide: the growing resistance of some harmful bacteria to the drugs that were intended to kill them.

Investigating exactly how bacteria learn to fend off antibiotics prescribed to treat infections is the subject of new research by Assistant Professor Brian G. Miller of FSU’s Department of Chemistry and Biochemistry and one of his graduate research assistants, Kevin K. Desai. They have found that bacteria are remarkably resilient to toxic substances, such as antibiotics, because bacteria have the innate ability to produce a large variety of proteins. Those proteins then are able to do things such as pump toxins out or alter toxins so that they can no longer kill the bacteria.

"Most of us take antibiotics to eliminate infections without considering what would happen if they failed to work,” said Kevin Desai, a graduate research assistant in Florida State's Department of Chemistry and Biochemistry. "While treating bacterial infections has typically been as easy as swallowing a pill,
researchers are apprehensive about the increasing frequency of infections that are resistant to antibiotics, and are searching for ways to regain the upper hand.”

In their study, Miller and Desai learned that about 2 percent of all the proteins produced by the model bacterium E. coli can be linked to enabling resistance to a single toxin called bromoacetate. Their research also has implications in elucidating the function of specific proteins and understanding how bacteria in the environment can survive in the presence of toxic manmade chemicals such as pesticides. A paper describing Desai and Miller’s work was published in the journal *Proceedings of the National Academy of Sciences*.

"The recent rise of antibiotic resistance demonstrates that bacteria are capable of rapidly evolving evasive strategies,” they wrote. "It also has exposed our lack of knowledge about the evolutionary processes leading to resistance.”

Understanding the mechanisms by which bacteria evade environmental threats has direct relevance for understanding and combating the rise of antibiotic resistance, Desai and Miller added. The techniques described in the paper will be highly useful for other researchers in the field because it will allow them to predict the resistance to specific antibiotics. Any resistance mechanisms identified could then be inhibited so that the antibiotics will retain their effectiveness.

**Journal Reference:**

By Jef Akst

**Insulin is key to kidney disease**

*A form of kidney disease may result from defective insulin signaling, challenging conventional wisdom*

[Published 5th October 2010 05:00 PM GMT]

Diabetic kidney disease likely results from defective insulin signaling in the kidneys, contradicting longstanding suspicions, according to findings appearing online today (October 5) in *Cell Metabolism*.

Scientists have long attributed this type of kidney disease—the leading cause of renal failure—to high glucose levels in the blood and defects in the kidney microvasculature.

The study "suggests there's a direct effect of insulin" on epithelial cells in the kidney, "which is really a new idea," said nephrologist Thomas Coffman of Duke University School of Medicine, who was not involved in the research. "I'm sure it will be a highly cited paper."

Diabetes causes numerous health problems, including a form of kidney disease known as diabetic nephropathy (DN). DN is characterized by protein in the urine, enlarged kidneys, and abnormalities in the glomeruli, specialized capillaries where the urine filtration process begins, and other parts of the kidney.

Researchers most often attribute the disease to defects in the microvasculature of the kidneys as a result of high blood glucose levels, which are known to be toxic to a variety of cell types. But growing evidence suggests that another cell type may be involved—epithelial cells known as podocytes. Furthermore, some people with insulin resistance accumulate protein in their urine, even when glucose is normal.

To investigate the role of podocytes and insulin signaling in the development of DN, a team led by molecular biologist and pediatrician Richard Coward of the University of Bristol in the UK examined two knockout mice models whose podocytes lacked the insulin receptor. Within 5 weeks of birth, the mice had developed abnormalities in their kidneys characteristic of human DN and protein had started accumulating in their urine, despite normal blood glucose levels. Their symptoms continued to worsen over the next 8 weeks.

"Our work suggests [DN] is not necessarily directly related to high glucose, but probably an insensitivity of that cell to insulin," Coward said. The mice were normal at birth, however, he noted, so insulin signaling in podocytes "doesn't seem to be that important for [kidney] development."
Notably, not all the symptoms of DN were present in the KO mice, suggesting other mechanisms may be important for the disease pathogenesis.

To examine how insulin signaling affects podocytes, the team examined the cells in vitro while adding varying amounts of insulin. They found that insulin alters the actin cytoskeletons of the cells, resulting in overall structural changes, including the retraction of cell projections that play a role in urine filtration. This restructuring process appears necessary to the normal function of the kidneys.

"What we think happens is that these cells are really dynamic, constantly remodeling and moving," Coward said. "With insulin, every time you have a meal, there's remodeling to brace itself for the increase in filtration load to the kidney." When insulin signaling is impaired, the cells fail to remodel, affecting their ability to filter proteins from the urine.

This is not the first paper to expand insulin's role in disease—scientists are finding more and more examples of major illnesses that may result from disruptions in the insulin signaling cascade. (See The Scientist's recent feature for the wide-reaching implications of this pathway.)

The results may also provide novel drug targets for the prevention or treatment of DN, suggested Coffman, who wrote an accompanying perspective. "This study suggests that the pathway of insulin [signaling] in epithelial cells is going to be important," he told The Scientist. "It does raise that as a pathway that could be targeted and probably should be targeted.”


comment:
INSULIN AND AGEING
by Nirmal Mishra, [Comment posted 2010-10-07 07:42:25]
Insulin modifies the structure of podocytes by altering the cytoskeletal elements in such a way that their microvilli are retracted. This might make the plasma membrane of these cells more compact, not allowing a huge elliptical protein, albumin to pass through. On the other hand, cells unresponsive to insulin might have projected microvilli causing the membrane to be porous enough so that albumin can pass through and finally find its way through tubules of the nephron to come in the urine.

Insulin is said to influence translation. Diminished insulin might not induce enough translational activities to produce enough receptors or receptor-like proteins or those proteins that pull down microvilli to render plasma membrane compact. The question is: why should podocyte microvilli be pushed up so as to create holes for albumin to pass through? What factors play that role? Are they related to ageing? How the steady-state equilibrium is is maintained between two opposing events?
Nirmal Kumar Mishra
Retd. University Professor of Zoology, Patna University, PATNA(INDIA)

comment:
Understanding Diabetic Nephropathy
by Vinod Nikhra, [Comment posted 2010-10-05 18:55:03]
An amazingly good article. Not all of the diabetic patients go on to develop the disease, only a percentage of them suffer from diabetic nephropathy and consequent renal failure. This fact may be explained by this study.

On the other hand, this may very well link the disease to underlying aging processes, one of them appears to be strongly linked to the insulin signaling, receptors and their metabolic arms.
Vinod Nikhra, M.D.
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www.nikhrafoundation.in

Rare Hybrid Cell Key to Regulating the Immune System
ScienceDaily (Oct. 11, 2010) — A cell small in number but powerful in its ability to switch the immune system on or off is a unique hybrid of two well-known immune cell types, Medical College of Georgia researchers report.

"This is actually the first cell we know of that has this type of appearance in nature," Dr. Andrew Mellor, molecular geneticist and immunologist who co-directs MCG’s Immunotherapy Discovery Institute, said of the cell that looks like a dendritic cell and a B cell but isn’t really either.

The discovery of this rare hybrid could have implications for the efficacy of new therapies that manipulate these two cell types to treat diseases such as cancer and rheumatoid arthritis.

When MCG scientists first reported the human equivalent of this cell in Science in 2002, they called it a subset of the dendritic cell that clusters in high exposure areas such as the gut but also roams the body, looking for invaders like a virus or cancer. Dendritic cells show their find to T cells, telling them to ignore or attack by bringing trash-eating macrophages, natural killer cells and the like into the fight.

What seemed most unique about the subset is its ability to express indoleamine 2,3 dioxygenase, or IDO, to turn off T cells. IDO is an enzyme used by fetuses and tumors alike to escape the immune response.

The new studies show that is only part of the cells’ distinctiveness. The cells also have the identifying markings of B cells, known for their ability to make antibodies against invaders. In fact, they found the
IDO-presenting cells came from the same precursor cell as B cells. But, when the scientists looked at mice missing B cells, they still found the IDO-producing cells. Hence, the cell didn’t need to produce antibodies to turn off T cells.

In reality, IDO-expressing cells have properties of both cells, said Burles A. Johnson III, an MCG M.D.-Ph.D. student and first author of the paper published in the *Proceedings of the National Academy of Sciences*. "It looks like a B cell and it’s not. It looks like a dendritic cell and it is and it isn’t," Johnson said.

While their studies are in mice, the cells also are in humans, showing up in some unfortunate places such as the drainage system for tumors, melanoma or even HIV where they likely help the diseases survive.

They also may be showing up in new dendritic cell therapies designed to strengthen the immune response to cancer. If the therapies happen to include some IDO-expressing cells, those could end up helping the cancer, said Mellor, the paper’s corresponding author. "All you need is a few of these cells in your dendritic cell vaccine and you don’t get stimulation any more, you get suppression," Mellor said.

Their confusing face could also cause hybrids to be lost in B cell-depleting therapies designed to lessen the immune system’s attack on joints in rheumatoid arthritis. "These therapies may also deplete IDO-expressing cells and decrease therapy effectiveness because you are eliminating cells that are there to help you," Johnson said.

"This gives us new insight into why these therapies might not be working as well as we think they might," Mellor added. Long-term goals include figuring out how to manipulate the hybrid’s activity to benefit patients.

**Journal Reference:**

**Cell Survival Protein Discovery Rewrites Immune System Story**

ScienceDaily (Oct. 10, 2010) — A discovery by Walter and Eliza Hall Institute researchers in Melbourne, Australia, reported in the journal *Science*, is set to rewrite a long-held belief about how the body’s immune system establishes its memory.

The findings of Dr Ingela Vikstrom and Associate Professor David Tarlinton, from the institute’s Immunology division, centre on immune cells called B cells that produce the antibodies which fight infection.

"B cells and antibody production are the key to the success of all currently used vaccines for immunity in humans," said Associate Professor Tarlinton. "It is therefore critical that we continue to develop our knowledge of the molecular interactions that lead to immune function, which are still only vaguely understood."

Memory B cells are essential for the long-lived immunity that arises after immunisation. To develop into memory cells, B cells have to survive the natural process of apoptosis, or programmed cell death, that occurs following a large immune response.

Associate Professor Tarlinton and Dr Vikstrom study the so-called pro-survival proteins that regulate B cell survival and are therefore responsible for instructing these cells whether to live or die.

Dr Vikstrom said that B cell memory arises in temporary cellular structures called germinal centres that develop in response to activation of the immune system.

"We used genetic and pharmacological methods to identify which pro-survival molecules were essential for the process of ‘instructing’ these cells to establish germinal centres, as well as instructing activated B cells to proliferate and differentiate into memory B cells," Dr Vikstrom said.

"We studied two well-known pro-survival proteins called Bcl-xL and Mcl-1, which we knew were involved in the process. It surprised us to find that, contrary to popular belief, Mcl-1 is the essential pro-survival protein required for creation and maintenance of B cell memory."

The finding contradicts the widely accepted theory in immunology circles that Bcl-xL is the major pro-survival protein responsible for sustaining the development of memory B cells.

The findings build on a paper Associate Professor Tarlinton and Dr Vikstrom published earlier this year in *Proceedings of the National Academy of the Sciences*, with institute researchers Dr Andrew Lew and Dr Emma Carrington. Using a molecule that blocked the action of Bcl-xL, the study revealed that Bcl-xL was not necessary for the development of germinal centres and memory B cells, indicating that another pro-survival protein—now shown to be Mcl-1—was the key to survival.
Mcl-1 is known to be an important survival protein for cancers. Associate Professor Tarlinton said the discovery could have repercussions for cancer treatment, as cancerous cells often arise from unregulated cell growth caused by defects in the apoptotic pathway. It could also have implications for the treatment of autoimmune disease and inhibiting transplant rejection.

"All cells have the potential to undergo apoptosis, so developing our understanding of the major proteins responsible for this process will have applications to all cell types in the body," he said.

Journal Reference:

New Survey on Sex in US, Biggest Since 1994
A special issue of the Journal of Sexual Medicine offers the most comprehensive national sexual behavior survey in more than a decade, researchers say.

The new data are based on a survey of a national probability sample of 5,865 people ages 14-94. Researchers with Indiana University’s Center for Sexual Health Promotion interviewed participants online with the help of Knowledge Networks from March to May 2009. Condom-maker Church & Dwight funded the study, called the National Survey of Sexual Health and Behavior, but its authors said the research integrity and data were unaffected.

Adolescent males reported condom use during 79.1 percent of the past 10 vaginal intercourse events, and adolescent females reported 58.1 percent for penile-vaginal intercourse (PVI). Condom use reported by men generally, however, was just 21.5 percent for previous 10 PVI, and an even lower 18.4 percent for all women. Among all men, condom use was 25.8 percent during the past 10 anal sex events, compared with 13.2 percent for women generally. Condom use during most recent anal intercourse was reported by 26.5 percent for insertive men, 44.1 percent of receptive men and 10.8 percent for receptive women.

The self-reported rate of condom use was generally higher for unmarried adults, while condom-protected PVI was greater among younger people, blacks and Hispanics, and those having PVI with a non-relationship partner. Statistically adjusted for these differences, condom use was significantly associated with fewer previous intercourse experiences with the partner and not using other forms of contraception. The lowest condom use rate was reported by men over 50.

"There’s been a major shift among young people in the role condoms have in their sexual lives," said Dr. Dennis Fortenberry, a pediatrics professor and lead author of the study’s section on teen sex.

Just 2 percent of adolescent boys had experienced sex in the past year, but that jumps to 40 percent among 17-year-olds. About 7 percent of adult women and 8 percent of adult men identified as gay, lesbian or bisexual, though the proportion with same-sex experience at some point in their lives was higher.

For additional information, the full survey data are published in a series in Journal of Sexual Medicine (2010;7(s5):255-373).

Australian Men's Sexual Practices in Saunas, Sex Clubs and Other Male Sex on Premises Venues
Sexual Health Vol. 7; No. 2: P. 186-192, (05.2010) Anthony Lyons; Anthony M.A. Smith; Jeffrey W. Grierson; Henry von Doussa
Although sex on premises venues (SOPVs) for men who have sex with men (MSM) have been implicated in the spread of STDs, little research has described men’s sexual encounters in these venues, particularly the degree to which men from different backgrounds engage in risky sexual practices.

In the current study, interviewers administered surveys to 186 MSM within 48 hours of visiting an SOPV. The MSM reported their sexual practices, the characteristics of their partners, and other circumstances regarding the encounter.

The study reported on 430 sexual encounters. Of the sexual encounters: 74.9 percent involved oral sex; 53.7 percent involved massage, frottage (sexual stimulation by rubbing against a person) or kissing; 36.3 percent involved solo or mutual masturbation; and 32.1 percent involved anal sex. In multivariate analyses, age was a significant factor for having protected anal sex (P=0.001), insertive anal sex (P=0.004), and receptive anal sex (P<0.001). These practices were found to occur more frequently in encounters among younger men, while masturbation (P=0.03) was more frequent among older men.
When the partner was affected by alcohol, the encounters were less likely to involve unprotected anal intercourse ($P=0.006$) and more likely to involve massage, frottage or kissing ($P=0.009$). In only 7.7 percent of encounters did men disclose their HIV status.

“With the likelihood of risky sexual practices varying according to background, results from this study should be used to guide interventions aiming to promote safer sex in SOPVs,” the authors concluded.

**Work Needed To Maintain Fight Against Polio In Nigeria**

"Nigeria's Expert Review Committee on Polio Eradication and Routine Immunisation has concluded that the country could stop poliovirus transmission by mid-2011 if it were to intensify and upgrade its eradication programme, and build on the significant progress it has made,” the Vanguard reports. This year Nigeria has experienced "one of the most dramatic reductions in poliovirus circulation seen in any endemic country," the article notes. According to UNICEF's Suomi Sakai, "We have reason to celebrate, but not to relax. Once polio is interrupted, it has to stay interrupted. We have to work together to make sure that all children in the country are protected routinely against polio and against other vaccine-preventable diseases like measles, diphtheria, pertussis and tetanus as well" (Obinna, 10/11).

**NIAID Awards Grant For Development Of Needle-Free Dengue Vaccine**

The National Institute of Allergy and Infectious Diseases (NIAID) has awarded a $15.5 million to two companies for the development of a needle-free dengue vaccine, using a technology that has been preliminarily tested on animals, in-PharmaTechnologist.com reports. The grant, awarded to Inviragen and PhramaJet to work in a five-year partnership, will cover "preclinical, regulatory filings, manufacturing and clinical testing of the needle-free dengue vaccine" (Taylor, 10/11). Denver Business Journal adds that needle-free technology, which delivers medicine through the skin, "removes hygienic and health concerns associated with the use and re-use of needles in poor countries" (Avery, 10/8). According to an Inviragen press release (.pdf), the needle-free technology will use the company's DENVax dengue vaccine, which is currently in Phase I testing for safety using the using the traditional needle and syringe (10/7).

**New River Blindness Diagnostic Test Developed**

Scientists have developed a new diagnostic test for river blindness or onchocerciasis, the Journal Sentinel's "Health and Science Today" blog reports. Diagnostic tests currently exist, but they often give false negatives and "are unreliable indicators of infection," said Judith Denery, a senior research associate at the Scripps Research Institute and lead author of the study, which was published in PLoS Neglected Tropical (Johnson, 10/7). To develop the test, researchers used a process known as metabolomics, "the systematic study of the unique chemical fingerprints that specific cellular processes leave behind," according to a Scripps Research Institute press release. "Ultimately this technology can be expanded for the diagnosis of other filarial and neglected tropical diseases," said paper co-author Kim Janda, a professor in Scripps' Departments of Chemistry and Immunology and Microbial Science (10/6).

**Calif. porn actor tests positive for HIV**

The Associated Press
Tuesday, October 12, 2010; 10:59 PM

LOS ANGELES—A porn actor has tested positive for HIV at a California clinic, setting off a scramble to track down partners who may have been exposed, and spurring two major production companies to suspend filming.

The actor was a patient of the Adult Industry Medical Healthcare Foundation, a San Fernando Valley clinic that caters to actors in the multibillion-dollar adult entertainment industry. The actor's identity and gender have not been released.

Clinic spokeswoman Jennifer Miller told the Los Angeles Times that efforts are under way to notify individuals who may have had sexual contact with the actor. Miller did not return calls or e-mail from The Associated Press on Tuesday.

Wicked Pictures and Vivid Entertainment told the Times that they stopped production as a precaution when the positive test was revealed.

Los Angeles County public health officials and state occupational health officials have said the widespread lack of condom use on porn sets puts performers at risk for contracting HIV and other
diseases. Major adult film producers, including Hustler’s Larry Flynt, have spoken out against the use of condoms in porn because viewers find them to be a turnoff.

Last year, a woman tested positive for HIV immediately after making an adult film, and in 2004, an HIV outbreak affecting several actors spread panic in the industry and briefly shut down productions at several California studios.

Porn actors are required by law to test negative for HIV and other sexually transmitted diseases within 30 days of going to work on a film.

State workplace safety officials at Cal/OSHA are considering strengthening rules designed to prevent transmission of disease through bodily fluids to specify the use of condoms in the adult entertainment industry.

Currently, the same laws that call on health care professionals to wear gloves and other protective barriers when dealing with patients applies to the adult film business, but the laws don’t make specific provisions for porn.

AIDS Healthcare Foundation President Michael Weinstein said his organization has been advocating for a tightening of the rules, and the adult entertainment industry and AIM clinic would "do everything in its power to prevent us from knowing who was impacted."

Weinstein said the latest case is the ninth HIV-positive adult film star to be treated at the AIM clinic since the 2004 outbreak.

Chief Counsel for Cal/OSHA Amy Martin said the clinic has been uncooperative in providing state regulators with key information by citing a patient’s federal right to medical privacy.

But the clinic has even refused to provide redacted copies of employment histories for infected actors, which would allow the state to investigate porn production companies without naming the sick patients, Martin said.

HIV is spread most often through sexual contact, but can also be contracted through sharing contaminated needles for drug use, infected blood products, or babies born to or breast-fed by infected women. It is the cause of AIDS, an immune disease that gradually destroys the body’s ability to fight illness.

Uganda: Nation to Produce New HIV Drug

Taddeko Bwambale
12 October 2010
Kampala — A new, more effective drug for treating HIV is to be manufactured in Uganda. The drug, under the generic name Tenofovir, will be produced by Quality Chemicals starting early next year.

Patients need only to take one pill once a day, as opposed to several drugs at time.

Tenofovir is said to be more effective than the current drug combinations in lowering the ability of the virus to multiply and infect new cells.

According to the plant’s chief commercial officer, George Baguma, the drug is safer and has no severe side effects, unlike most HIV drugs on the market. Some drugs used in antiretroviral treatment, such as Stavudine have been phased out due to their severe side effects.

Baguma said the company was in the process of registering the drug with the National Drug Authority. He, however, said production of the drug awaited a review by the Government of the existing guidelines of antiretroviral treatment.

He was speaking at a function to celebrate the plant’s 3rd anniversary at Luzira on Friday.

The company currently manufactures antiretroviral drugs and anti-malarial drugs and supplies them to the Government.

It is the first plant in sub-Saharan Africa to receive pre-qualification certification by the World Health Organisation to produce HIV drugs.

Baguma said the company was awaiting inspection results from the Kenya Drug and Poisons board to start supplying drugs to Kenya.

He also said a new plant would be built to increase production, and that systems had been installed for the production of Tenofovir.

Tenofovir belongs to a class of drugs known as nucleotide reverse transcriptase inhibitors, which decrease the viral load in the blood and lower the risk of contracting other diseases such as cancer.

A monthly dose of the drug will cost about sh44,000 ($20), much lower than the monthly cost of the same drug in Europe, which is about sh1.4m ($600).
China court hears first HIV discrimination suit
Published: 13/10/2010 at 02:58 PM

A Chinese court on Wednesday heard the case of a man who alleges he was denied a job because he is HIV-positive, in the nation's first such discrimination case, his lawyer said.

A Chinese court was Wednesday to begin hearing the case of a man who alleges he was denied a job because he is HIV-positive, in what state media has said is the nation's first such discrimination case.

The plaintiff, who has only been identified by his alias Xiao Wu, filed the suit against the education department of Anqing city in the eastern province of Anhui.

The lawsuit alleges city officials denied the plaintiff, a recent college graduate, a teaching job after a medical screening for illnesses including syphilis and hepatitis C revealed he had HIV, the virus that causes AIDS.

The screening was conducted after he had already passed written tests and interviews, state media has reported.

"We're quite optimistic about this case... because this is the first case related to HIV and guaranteeing employment rights," lawyer Li Fangping told AFP, adding that the judgment would only be announced after a 10-day period.

"If we lose the lawsuit, then the very authority of the Employment Promotion Law will be challenged because it contains a clear rule that (employers) cannot violate a person's employment rights because he or she carries a disease."

The plaintiff is asking for the education department to give him the job, state media has said.
Li said the department had defended itself by saying the decision was made "with the interests of the students and the public in mind."

AIDS has long had a heavy stigma attached to it in China, with sufferers forced to hide their condition. However, there have been recent signs that attitudes are changing.

The government has started talking more openly about HIV prevention and control in China, though people with HIV/AIDS still encounter huge discrimination in employment, education and healthcare.
China says that at least 740,000 people are living with HIV but campaigners say the actual figure could be far higher.

The head of UNAIDS, Michel Sidibe, warned last year that 50 million people in the country were at risk of contracting the AIDS virus, mainly through unprotected sex or the sharing of needles.
Despite signs of openness, the hassling of some independent campaigners and organisations has nevertheless continued.

High-profile activist Wan Yanhai, whose group helped uncover a major tainted blood-selling scandal in the 1990s, fled to the United States with his family earlier this year because he said he feared for his safety.

Condom Negotiation Strategies and Actual Condom Use Among Latino Youth
Journal of Adolescent Health Vol. 47; No. 3: P. 254-262, (09..2010) Jeanne M. Tschann, PhD; Elena Flores, PhD; Cynthia L. de Groat, MA; Julianna Deardorff, PhD; Charles J. Wibbelsman, MD

Determining which condom negotiation strategies are effective in obtaining, or avoiding, condom use among Latino youths was the goal of the current study.

The subjects—694 Latino youths, ages 16 to 22, 61 percent female—were interviewed about condom negotiation strategies, perceptions of whether their partner wanted to use condoms, and actual condom use. Three strategies to obtain condom use—risk information, direct verbal/nonverbal communication, and insisting—were examined, as were four strategies for avoiding condom use—emotional coercion, ignoring condom use, disliking condoms, and seduction. Multiple linear regression was used to analyze the data, which included 574 youths who said they wanted to use or avoid using condoms.

Nearly 60 percent of the youths reported they wanted to use condoms, and nearly all these employed some strategy to obtain condom use. Compared to young women, young men who said they wanted to use condoms were more likely to do so. Risk information and direct verbal/nonverbal communication were effective strategies for obtaining condom use, even among youths who perceived their partners did not want to use condoms. Ignoring condom use was an effective avoidance strategy, even when youths thought their partners wanted to use condoms. In an unexpected finding, young men who expressed disliking condoms had higher condom use rates than young men not using this avoidance strategy.
“This research identified condom negotiation strategies that are effective among Latino youth, even when they believe their partners do not want to use condoms,” the authors concluded. “Health care providers could encourage Latino youth to use such condom negotiation strategies.”

Reducing HIV Risk Behavior of Men Who Have Sex with Men Through Persuasive Computing: Results of the Men’s INTrernet Study-II


In the United States and similar countries, men who have sex with men (MSM) continue to be the group at highest risk of HIV/AIDS. “As the Internet becomes popular for seeking sex, online interventions to reduce sexual risk are critical,” noted the authors, who undertook the current study to develop and test a highly interactive Internet-based HIV prevention intervention for MSM. A secondary objective was to demonstrate that good retention is possible in online trials.

The study was designed as a randomized controlled trial with three-, six-, nine-, and 12-month follow-up. In the research, which was conducted in 2008, 650 participants were randomized to an online, interactive risk reduction intervention or to a waitlist null control group.

During the 12-month period, retention was 76 percent to 89 percent. Compared to the control group at three-month follow-up, the intervention group showed a 16 percent reduction in reported unprotected anal intercourse (95 percent confidence interval [CI] of rate ratio: 0.70-1.01). No meaningful differences were noted at 12-month follow-up.

“Internet-based, persuasive computing programs hold promise as an effective new approach to HIV prevention for MSM, at least in the short term,” the authors concluded. “Further, online trials can be conducted with acceptable retention provided strong retention protocols are employed. Four directions for future research are identified.”

West African Cholera Epidemic Exacerbated By Flooding; More Than 1,800 Deaths Reported

The WHO "says 1,879 deaths have been reported" from cholera in Nigeria, Chad, Cameroon and Niger, the Associated Press reports. "The wave of cholera started a few months ago" and "nearly 40,500 cases have been reported in the region so far. Nigeria alone has experienced nearly 1,200 deaths," its worst cholera outbreak in two decades," according to the article (10/12).

U.N. News Centre adds that UNICEF "and its partners have already scaled up their activities in Chad, which is facing one of its worst cholera epidemics in 10 years, with nearly 2,600 cases and 112 deaths reported as of the start of the month. Cholera kits have been donated to hospitals and non-governmental organizations (NGOs), and technical assistance provided to the health ministry" (10/12).

"The U.N. says flooding in the region, as well as poor hygiene conditions and populations movements, have contributed to the 'unusually high incidence of cholera,'" the AP writes (10/12).

"Nearly 1.5 million people have been affected by floods and 377 killed in Western and Central Africa," U.N. News Centre reports. Benin, which has been "hardest hit," has declared a state of emergency and "appealed for international aid." Burkina Faso has "launched a $14 million emergency plan and has received $2 million from the U.N. Central Emergency Response Fund." Under-Secretary-General for Humanitarian Affairs Valerie Amos is expected to visit the region to meet with relief organizations and local authorities and "a U.N. Disaster Assessment and Coordination team will probably leave for [Benin] tomorrow" (10/12).

A crucial link in immune development and regulation unearthed

An Australian team of scientists has uncovered a quality control mechanism that must take place for our immune system to subsequently effectively destroy harmful viruses and bacteria.

The findings were published today in the prestigious international journal Nature.

The team solved a 15-year puzzle by working out the structure and function of a protein called pre T alpha that is essential in guiding the correct expression of various receptors expressed by T lymphocytes, white blood cells of the immune system.

These receptors, known as T cell receptors, recognise unique components of microbial pathogens. Joint team leader, ARC Federation Fellow Professor Jamie Rossjohn, from Monash University’s School of Biomedical Sciences, said that understanding the structure of pre-T alpha explains a fundamental step in T cell development and anti-microbial immunity.
"We showed that the pre-T alpha molecule not only assists in the expression of functional T cell receptors but it also allows two molecules to bind together, which alerts the T cell that this receptor is constructed properly, allowing the T cell to move to the next step in its development," Professor Rossjohn said.

Co-leader of the project Professor Jim McCluskey from the University of Melbourne said without T cell receptors we would be profoundly immunodeficient and therefore pre-T alpha plays an essential role in ensuring proper immunity.

"Additionally, there is some evidence that pre-T alpha may also be involved in some childhood leukaemias, so this new knowledge of how it functions may be important in diagnosis and treatment of acute lymphoblastic leukaemia," Professor McCluskey said.

**Adding drugs to already successful HIV treatment doesn’t reduce viral load further**

*Published: 15 October 2010*

Intensifying effective HIV therapy with the addition of an extra drug that crosses the blood-brain barrier does not reduce residual levels of viral replication in cerebrospinal fluids or the blood, an international team of investigators report in the online edition of the *Journal of Acquired Immune Deficiency Syndromes*.

The researcher also found that patients continued to have evidence of immune activation and inflammation in the brain.

“Treatment intensification with a potent CNS [central nervous system]-penetrating antiretroviral drug does not reduce residual CSF [cerebrospinal fluid] HIV RNA levels or intrathecal immune activation”, write the investigators.

Effective combination antiretroviral therapy has dramatically reduced rates of illness and death in patients with HIV. Recent advancements in antiretroviral treatment mean that an undetectable viral load is a realistic goal for the vast majority of patients.

When treatment first became available in 1996 there were initially hopes that long-term suppression of HIV in the blood would eventually lead to eradication of the virus. However, it soon became apparent that HIV levels in blood were being repopulated from latent CD4 cells that were infected with the virus.

Moreover, ultrasensitive viral load tests have shown that the majority of patients taking treatment continue to have very low levels of HIV in their blood.

Residual viral load (2 to 20 copies/ml) has also been observed in the cerebrospinal fluid of individuals with undetectable blood viral loads. In addition, many patients taking HIV therapy, even if taking drugs capable of crossing the blood-brain barrier have evidence of intrathecal immune activation and inflammation.

Because of these findings, investigators wished to see if adding an extra antiretroviral drug to regimens that were already suppressing viral load would reduce residual HIV levels in the cerebrospinal fluid and immune activation and inflammation in the brain.

Their study involved ten patients. These individuals had had an undetectable blood viral load (below 50 copies/ml) for a median of 6.5 years. Their median CD4 cell count was 465 cells/mm$^3$, eight were men and their average age was 52.

The study lasted eight weeks. Lumbar punctures were performed on entry to the study, at baseline, after four weeks of treatment, and again at the end. Viral load was measured in cerebrospinal fluid and markers of intrathecal immune activation and inflammation were also monitored.

Treatment was intensified by the addition of either maraviroc (*Celsentri*) or lopinavir/ritonavir (*Kaletra*), both of which have good penetration into the central nervous system, or with T-20 (enfuvirtide, *Fuzeon*), which does not.

During the first four weeks of the study, the patients received a brain-penetrating drug, after which they switched to T-20.

At baseline, median blood viral load was 5 copies/ml, and median viral load in cerebrospinal fluids was 2 copies/ml. Immune activation or inflammation in the brain was evident in the majority of patients.

Intensification of therapy did not further reduce residual viral load levels in cerebrospinal fluids which remained unchanged through the eight weeks of the study. Seven patients had detectable viral load in this compartment at least once. Viral load in blood was also unaffected, as were markers of intrathecal inflammation and immune activation.

Concentrations of maraviroc and *Kaletra* were well within their therapeutic ranges, and maraviroc was detectable in the cerebrospinal fluids of seven patients.
“We show that treatment intensification has no effect on either residual CSF HIV RNA levels or intrathecal immune activation over the course of 4 weeks with an antiretroviral drug that penetrates in the CNS”, comment the authors. “We could not detect any significant changes in the level of residual plasma viremia during the total treatment intensification period of 8 weeks.”

The investigators do not believe that their findings have any immediate implications for HIV care. Rather, they are of interest regarding “HIV persistence and reservoirs...these findings argue against the hypothesis that ongoing cycles of viral replication are the main source of residual CSF viremia and intrathecal immune [activation].”

Reference
Yilmaz AY et al. Treatment intensification has no effect on the HIV-1 central nervous system infection in patients on suppressive antiretroviral therapy. J Acquir Immune Defic Syndr, online edition, 2010 (link to abstract and paid for full text).

MTV’s ‘16 and Pregnant’ Series Hailed a Cold Shower for Teens
As it enters its third season, MTV’s “16 and Pregnant” is emerging among both adults and youth as a cautionary tale on the risks of teen sex.

“16 and Pregnant” is a reality-based show that follows several young women through their pregnancies and deliveries. The unvarnished stories have been described as heart-rending and gritty.

“One could make the argument that these are the best teen-pregnancy prevention public service announcements ever made,” said Bill Albert, chief program officer for the non-profit National Campaign to Prevent Teen and Unplanned Pregnancy (NCPTUP).

Teens responding to a recent poll sponsored by NCPTUP appear to agree with Albert. About 60 percent of 1,008 teens surveyed had seen the show, and about 82 of these said the show illustrated the realities of raising a child.

Overwhelmingly, the teens said appealing TV shows and characters inspired them to think about how to avoid pregnancy themselves. Among girls, 80 percent said they “agree strongly” or “agree somewhat,” while the comparable percentage among boys was 67 percent.

Still, 15 percent of teens in the poll said it glamorized having a baby in high school, a position held by the Parents Television Council, a media-watchdog organization. “16 and Pregnant” has inspired a spin-off, “Teen Mom,” that documents the first years of young motherhood and launched several of its subjects onto magazine covers.

“Certainly, when you see the stars of that program being featured on teen magazines, it turns from cautionary tale into something that looks almost glamorous to the outside observer,” said Melissa Henson, director of communications for the organization.

NCPTUP supports the series and even supplies discussion guides for each episode of “16 and Pregnant.” The series is “gritty, not glamorous; sobering, not salacious,” said Sarah Brown, chief executive of the National Campaign.

Prevalence of Sexually Transmitted Infection/Human Immunodeficiency Virus Counseling Services Received by Teen Males, 1995-2002
Journal of Adolescent Health Vol. 46; No. 6: P. 553-559, (06..2010) Arik V. Marcell, MD, MPH; David L. Bell, MD, MPH; Laura D. Lindberg, PHD; Adel Takruri
The authors set out to determine whether improvements have been made in the delivery of sexually transmitted infection (STI) and/or HIV counseling services to teenage males.

Analysis was performed on data from two nationally representative surveys of 15- to 19-year-old males: the 1995 National Survey of Adolescent Males (n=1,729; response rate=75 percent) and the 2002 National Survey of Family Growth (n=1,121; response rate 78 percent). The main outcome measure included an STI/HIV discussion with a doctor/nurse. The association of outcome measures and survey year among males reporting various types of sexual behaviors (e.g., varying partner numbers, higher-risk sex), unadjusted and adjusted for socioeconomic and health care access factors, was examined by weighted bivariate and multivariate Poisson regression analyses.

In 2002, one-third of males who reported three or more female partners, anal sex with female partners, or oral/anal sex with male partners said they had received STI/HIV counseling. Among males reporting high-risk sex (e.g., sex with prostitute, person with HIV or often/always high with sex), only 26 percent said they had received counseling. Even after controlling for sociodemographic and health care access factors, no improvements in STI/HIV counseling were found between 1995 and 2002.
“Mechanisms are needed to raise the importance of STI/HIV counseling services among sexually active male teens as well as to improve health care providers’ delivery of these services,” the authors concluded.

**Trends in the Location of the HIV-Positive Population in Australia: Implications for Access to Health Care Services and Delivery**

*Sexual Health* Vol. 7; No. 2: P. 154-158, (05..2010)  Marina Carman; Jeffrey Grierson; Marian Pitts; Michael Hurley; Jennifer Power

Assessing existing and potential trends in the HIV-positive population in Australia is important for current and future health care service development and delivery, the authors noted in their introduction.

The current study provided a new analysis of existing data on this population from the “HIV Futures 5” survey, which comprised responses from 982 HIV-positive Australians from all states and territories. The analysis involved a geographic breakdown of respondents based on area type—capital city or inner suburban, outer suburban, regional center and rural—with patterns of health care service access. The researchers also calculated the distance between the postcode of the respondent’s residence and that of the doctor providing HIV services. They further conducted an analysis of area type by income and age.

In the area-type analysis, important differences were noted in patterns of access to antiretroviral prescriptions and choice of provider for HIV-related and general health care. Compared to those living in regional centers, those living in outer suburbs reported traveling a longer median distance to see a doctor for HIV-related care.

“Differences in service use appear to be related to geographic accessibility of different service types,” the authors concluded. “However, there may be other important social, economic and cultural factors involved. Aging and socioeconomic pressures may be influencing a move away from inner suburban areas where most HIV-specific care is located. This new analysis assists in finding the right balance between increasing the accessibility of HIV-specific services and ‘mainstreaming.’ Longitudinal data collection would further assist in tracking trends in geographic location, and how often and at what intervals people living with HIV utilize health care services.”

**Highly Pathogenic Bird Flu Virus Can Survive Months on Steel or Glass at Cooler Temperatures**

ScienceDaily (Oct. 14, 2010) — On the eve of the 2010-11 influenza flu season, scientists and engineers have identified the environmental conditions and surfaces that could enable a highly pathogenic (H5N1) bird flu virus to survive for prolonged periods of time—at least two weeks and up to two months. Among them: The virus appears to thrive at cooler temperatures and low humidity. The study, which could lead to new strategies for preventing the flu virus from spreading, appears in ACS’ *Environmental Science & Technology*.

Joseph Wood and colleagues note that the highly pathogenic (H5N1) avian influenza virus so far has been rare but dangerous in humans, with mortality rates of about 60 percent. Although the H5N1 virus may spread to humans by direct contact with infected birds or other virus-contaminated material, health experts are concerned that the virus could evolve to develop the ability to spread from person to person, and cause serious outbreaks. However, there is little information on how different environmental conditions and materials affect H5N1’s survival.

The scientists investigated the ability of a strain of highly pathogenic H5N1 originating from Viet Nam to survive on a variety of materials under different environmental conditions, including changes in temperature, humidity, and simulated sunlight. The materials included glass, wood, steel, soil, and chicken feces. They found that H5N1 survived longer (up to two weeks) at cooler temperatures—around 39 degrees Fahrenheit—but lasted only up to one day at room temperature. The virus also tends to persist at low humidity and no sunlight and on certain surfaces, including glass and steel. Although when exposed to simulated sunlight, the virus survived longer on soil and chicken feces compared to the other materials. It could potentially survive for up to two months on those materials, they estimate.

At low temperatures and low humidity, the virus actually survived longer on steel, glass, and soil than in chicken feces, a common source for spreading the virus. "Measures taken to contain and inactivate the virus, especially in these areas or conditions, may be warranted," the article notes.

Journal Reference:
Virus Deadly in Livestock Is No More, U.N. Declares
By DONALD G. McNEIL Jr.

In only the second elimination of a disease in history, rinderpest — a virus that used to kill cattle by the millions, leading to famine and death among humans — has been declared wiped off the face of the earth.

Rinderpest, which means “cattle plague” in German, does not infect humans, though it belongs to the same viral family as measles. But for millenniums in Asia, Europe and Africa it wiped out cattle, water buffalo, yaks and other animals needed for meat, milk, plowing and cart-pulling.

Its mortality rate is about 80 percent — higher even than smallpox, the only other disease ever eliminated.

“This is something the entire global community can be proud of,” said Dr. William R. White, director of the United States Department of Agriculture’s foreign animal disease diagnostic laboratory on Plum Island, N.Y. “Rinderpest has caused almost unimaginable misery for a very long time.”

The last case was seen in Kenya in 2001. On Thursday, the United Nations Food and Agricultural Organization announced that it was dropping its field surveillance efforts because it was convinced that the disease was gone. The official ceremony in which the World Organization for Animal Health will declare the world rinderpest-free is scheduled for May. (That organization, known as the O.I.E. for its initials in French, was created in 1929 chiefly to fight rinderpest.)

“This has been a remarkable achievement for veterinary science, evidence of the commitment of numerous countries,” the Food and Agricultural Organization said in its statement.

Still to be decided is how much virus to keep frozen in various countries’ laboratories, along with tissue from infected animals and stocks of vaccine, which is made from live virus. Virologists like to have samples handy for research, but public health experts, fearing laboratory accidents or acts of terrorism, usually press to destroy as much as possible. The smallpox virus is officially supposed to exist only in two lab freezers, one in Atlanta and one in Moscow.

Rinderpest is thought to have originated in Asia and spread through prehistoric cattle trading; it was in Egypt 5,000 years ago. It never became established in the Americas (though there was a small outbreak in Brazil 90 years ago), nor in Australia or New Zealand. Cattle infected with it would have started dying aboard ship and the herd would be slaughtered or quarantined on arrival.

But it reached Africa in the late 19th century, with devastating consequences. The near total destruction of herds meant widespread famines; in one of those, a third of the population of Ethiopia died, according to the Food and Agricultural Organization.

It was apparently introduced to Abyssinia, which is now Ethiopia, in cattle from India imported by the Italians during their campaign to conquer Abyssinia, said Dr. Jeffrey M.B. Musser, a rinderpest expert at Texas A&M’s veterinary school. Some experts believe it was deliberate, as a form of biological warfare, he said, while others contend that it was accidental.

It also infected game animals, like giraffes and antelopes, but did not kill as many of them.

For centuries, cattle owners and local veterinary officials fought the disease with slaughter, quarantine and crude immunization efforts. As with smallpox, many tried “inoculation” — cutting open the skin and introducing pus or tissue from infected animals, sometimes treated with heat or chemicals, hoping to cause minor infections that would create immunity. But these efforts sometimes just spread the disease.

Then in the 1950s, Walter Plowright, a British veterinary pathologist working in Africa, developed a successful vaccine using live, weakened virus produced with the same cell-culture techniques pioneered for polio.

The global effort to eliminate rinderpest was officially begun in 1994. It relied on the vaccine and a network of field agents and laboratories that could hunt for and confirm outbreaks.

Nine years passed between the last known case and this week’s de facto declaration that the disease was gone, but such timelines are typical in disease eradication. Many diseases resemble one another, and the authorities need both time and frequent blood testing to be sure one is really gone. The last case of smallpox was seen in Somalia in 1977, but the disease was not declared eradicated until 1980. (In April, there was a brief scare in Uganda when doctors reported a new case; it turned out to be chicken pox.) Veterinary diseases need longer surveillance; while mothers will carry sick children many miles to a doctor, herders often just have to let animals die.
The virus that caused a worldwide outbreak in 2002 of SARS, or severe acute respiratory syndrome, was effectively contained by mid-2003. The last known case, caused by a lab accident, occurred in 2004, but SARS is not considered eliminated because it is assumed to persist in bats, wild civets and perhaps other animals, and could return.

By Kerry Grens

**Scientist as subject**

By a fortuitous twist of genetic fate, a small percentage of humans, roughly one in 100, are able to resist infection to HIV. Wouldn’t it be even more fortuitous if one of these exceptional people, prized by scientists as walking exemplars of what a therapy might ultimately accomplish, happened to be an AIDS researcher as well? Meet James Hoxie, director of the Penn Center for AIDS Research at the University of Pennsylvania.

“I give lots of blood and still do,” Hoxie says in his office, surround by tropical plants, books, and diagrams of viral envelope proteins. “I think I’ve been asked to give seminars at places just so people could bleed me,” he laughs.

Hoxie didn’t know he was a carrier for the crucial mutation until he had been elbow-deep into AIDS research for years. Since the mid-1980s researchers, including Hoxie’s group, had been hunting for the coreceptor on CD4 cells that allows the virus to enter a cell. After a decade in pursuit, five papers fired out results in rapid succession. The answer to part of the puzzle was CCR5.

Robert Doms’s team at the University of Pennsylvania was one of those that successfully identified the CCR5 coreceptor in collaboration with a group in Belgium. “A cool thing then was that they started looking for mutations right away,” Doms recalls. Doctors knew some people were able to ward off infection, and Doms’s colleagues wanted to see whether CCR5 was responsible. Shortly after CCR5 was identified, so were a few people who carried a deletion in the gene—called delta32—that crippled the protein and blocked HIV entry. Doms started his own search for carriers in Philadelphia.

“I think I’ve been asked to give seminars at places just so people could bleed me.”

Hoxie remembers providing Doms’s staff a cheek swab one morning. Reaction to the results was swift. “I knew something was up when I saw five people standing outside my door in the afternoon with needles and tubes, asking for blood,” he says. It turns out Hoxie is homozygous for the mutation. Word spread quickly among the community of this new source of HIV-resistant cells.

“It’s useful for controls,” says John Moore at Cornell University, because cells with delta32 will show whether a virus is absolutely dependent on CCR5 for entry. Hoxie is often thanked at the end of papers for contributing blood. Moore sends him bottles of wine.

More than a decade later, Hoxie’s blood is still in circulation among HIV researchers. Carl June at the University of Pennsylvania includes it as a positive control in studies to manipulate the immune system of people infected with HIV, using a gene therapy technique. “In principle [we’re working] to convert people to have the same resistance that Jim does,” June says.

Hoxie occasionally taps his vein for his own controls in probing how the virus escapes the immune system. “Getting rid of CCR5 makes things simpler,” he says. Hoxie is perhaps best known for identifying HIV isolates that are able to infect immune-system cells other than CD4. His current research focuses on the basic biology and structure of viral envelope glycoproteins and how they mediate viral entrance into the cell. Ultimately he’d like to see his work contribute to an HIV vaccine.

Doms has recently extracted Hoxie’s blood and subsequently knocked out the second CD4 coreceptor, CXCR4, to create even more resistant immune-system cells, which he has transplanted into mice.

Homozygotes like Hoxie have demonstrated an immune property vital to the development of therapy: Their immune systems are still perfectly healthy, despite the absence of CCR5. In 2007 the Food and Drug Administration approved Pfizer’s CCR5 blocker, maraviroc, as an HIV drug. Moore is researching ways to use CCR5 inhibitors for preventing infection. “The importance of CCR5 plays out in all kinds of ways,” Hoxie says.

June’s approach is viral eradication—replacing an infected immune system with an uninfected one that also carries the delta32 mutation. While June is currently enrolling people in human clinical trials, in 2008 researchers in Germany took a slightly different tack to reach essentially the same endpoint. A person (known as The Berlin Patient) who was infected with HIV and also had leukemia received a bone marrow transplant from a delta32 homozygote. The patient stopped antiretroviral therapy, and the virus has not returned. “This is rocking the planet,” Hoxie says. “It’s an incredibly exciting thing.”
June says Hoxie’s willingness to roll up his sleeve and donate blood has made it convenient to do his research. “What’s more important is Jim is a great scientist,” June says. “That’s his real importance.”

**NIH Scientists Researching HIV Vaccine Develop Method for Preserving Virus Fragment Shape**

“A strategy for designing ... [an HIV] vaccine involves identifying the key viral surface structures, snipping them off and developing a method to present these fragments to the immune system. When some parts of the surface of HIV are removed, however, they change shape such that antibodies no longer recognize and bind to them. A research team led by investigators at the Vaccine Research Center of the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, has developed a strategy to overcome this problem. The strategy has implications for scientists designing vaccines for HIV/AIDS as well as for other viral diseases.

“The team has fashioned a technique for extracting an antibody-recognizable portion of the surface of a virus and placing this surface fragment, known as an epitope, into a computer-designed protein scaffold. The scaffold locks the epitope in the shape recognized by the immune system. ... “The NIAID researchers are continuing to refine this technique and apply it to the design of vaccines for HIV/AIDS as well as other infectious diseases.”

By Jennifer Welsh

**Dr. James’s Fever Powder, circa 1746**

Dr. James’s fever powder, patented by English physician Robert James, claimed to cure fevers and various other maladies, from gout and scurvy to distemper in cattle. Though its efficacy was often questioned, the powder had “a long tradition of usage,” from its introduction in 1746 well into the 20th century, says John Crellin, a professor of medical humanities at Memorial University of Newfoundland. It was even prescribed to King George III when he was suffering from cataracts, rheumatism and dementia at the end of his life.
1—To safeguard his secret formula for the fever powder, James submitted a fake patent application that didn’t reveal the proper way the powder was created and formulated. The true composition of Dr. James’s powder was in question for many years, and was believed to be continually changing throughout its production. Determining its formula “was a challenge to the growing field of analytic chemistry,” says Crellin.

2—When James died in 1776, his manufacturing and marketing partner John Newbery inherited the patent and continued to sell the powder. As a notable English publisher, Newbery would advertise the powder in his books and had his son-in-law Christopher Smart dedicate many of his poems to James. The medicine was even included in the story line of the book Goody Two-Shoes by Oliver Goldsmith, an Irish poet, physician and friend of Newbery’s, in which the heroine’s father dies when he is “seized with a violent fever in a place where Dr. James’s Powder was not to be had.”
3—In 1791 George Pearson, a respected doctor and chemist of the time, determined that the powder was made of a mix of antimony and calcium phosphate. Because antimony is a toxic substance, the powder was deemed a contributing factor to the death of author Oliver Goldsmith in 1774.

4—In addition to single-use packets, the medicine was also one of the first to be distributed in a multidose bottle.

1 in 22 Blacks Will Get HIV, CDC Report Says
A new CDC report estimating the lifetime risk of HIV diagnosis for several populations found great disparities by racial/ethnic groups. Based on HIV surveillance, vital statistics, and census data from 37 states and Puerto Rico for 2007, an estimated 4.65 percent of blacks/African Americans would receive an HIV diagnosis during their lifetime, or 1 in 22, according to the new report.

The 1 in 22 risk was more than twice the estimated lifetime risk of HIV diagnosis for Hispanics/Latinos (1.92 percent, or 1 in 52) and eight times that of whites (0.59 percent, or 1 in 170), the report found.

The estimates of lifetime risk of HIV diagnosis are not representative of all HIV diagnoses in the United States. However, the data also were not considered unusual. A report published in 2008 found a similar high estimated lifetime risk of HIV diagnosis for blacks.


New HIV Cases Top One Thousand Again
Australian Associated Press, (10.18.2010) Danny Rose
New diagnoses of HIV in Australia reached 1,050 in 2009, the continuation of a decade-long climb and the highest figure in almost two decades.

“It’s fair to say over the last decade there was a substantial increase and we are starting to stabilize out, just recently,” said Dr. David Wilson, of the National Center in HIV Epidemiology and Clinical Research.

The climb in HIV diagnoses comes amid mixed success in addressing other STDs. Chlamydia diagnoses rose 4 percent in 2009 to 62,613. At the same time, rates of gonorrhea and syphilis improved as did the incidence of hepatitis C. Among those 15 to 19 years of age, a drop in injecting drug use is credited with lowering cases of hepatitis C by 80 percent in the last five years.

Wilson attributed the rise in HIV diagnoses to the fact that improved treatment has made the disease “not as scary as it was in the 1980s.”

While HIV diagnoses are increasing, mortality from HIV has declined since the 1990s. In 2009, nine deaths in Australia were attributed to AIDS, down from 26 in 2008.

“We are in an era where we are seeing the lowest deaths associated with HIV than we have seen in history,” Wilson said.

About 25 percent of the HIV-positive population is 55 or older, compared to 2.5 percent in 1985 and the 44 percent expected in 10 years, Wilson said.

Interventions for Young People in Australia to Reduce HIV and Sexually Transmitted Infections: A Systematic Review
Sexual Health Vol. 7; No. 2: P. 107-128, (05.2010) Melissa Kang; Rachel Skinner; Tim Usherwood
The current study comprises a review of intervention programs that aim to reduce the burden of HIV and other STIs among young people in Australia.

After identifying articles from seven databases, the team reviewed intervention studies set in Australia and involving persons ages 12 to 25. They then developed a two-dimensional matrix consisting of “setting” and “intervention type” to categorize each study.

Most of the 42 studies that met the inclusion criteria were uncontrolled intervention studies. Twenty-three of the studies measured participation in chlamydia ± other STI testing; the highest participation rates were found in non-clinical and non-general practice health care settings. Four studies facilitated
access to testing indirectly through the Internet or other media. Ten involved the provision of education and measured its impact on factors such as knowledge, attitudes and/or behavior. Three involved novel immunization strategies for either hepatitis B vaccine or human papillomavirus vaccine. Two studies assessed the impact of enhanced STI surveillance programs on STI prevalence rates.

“Proactive STI testing in non-clinical and some health care settings appears feasible and achieves higher testing rates than in general practice; however, more evaluation of testing strategies in general practice settings is required,” the authors concluded. “New technologies such as the Internet and [Short Message Service] are useful adjuncts for influencing behaviors such as condom use and STI testing. Media campaigns that promote STI testing can have a positive impact on testing rates.”

Analysis indicates a third H1N1 pandemic wave unlikely in 2010
Analysis of H1N1 antibody levels (seroprotection rates) after the 2009 pandemic suggest that a third wave is unlikely in 2010, although adults over age 50, particularly those with chronic conditions, should be immunized for the fall flu season, states a research paper in *CMAJ (Canadian Medical Association Journal)* (pre-embargo link only) [http://www.cmaj.ca/embargo/cmaj100910.pdf](http://www.cmaj.ca/embargo/cmaj100910.pdf).

The study, by researchers from the BC Centre for Disease Control, University of British Columbia and BC Biomedical Laboratories, compared blood levels of antibodies against the H1N1 influenza before and after the 2009 pandemic. They looked at 1127 people in British Columbia’s Lower Mainland aged 9 months to 101 years.

Samples collected before the pandemic indicated that less than 10% of children and adults under age 70 had protective levels of H1N1 antibodies whereas 77% of people over age 80 had protective levels. In follow up after the waves of infection and the fall 2009 immunization campaign, the researchers found a 70% protection rate in people under age 20 but lower seroprotection rates in adults aged 20-49 (44%) and 50-79 years of age (30%). People aged 70-79 years had the lowest rate of antibodies (21%) whereas those over 80 years had higher rates.

"The higher percentage with seroprotection we observed in the young may have resulted from higher pandemic H1N1 infection rates and earlier prioritization of pandemic H1N1 vaccine to young children," writes Dr. Danuta Skowronski, BC Centre for Disease Control and University of British Columbia with coauthors.

They estimate that a community-level protection above 40% would be enough to prevent a large epidemic in a population, especially if school-age children who generally contribute most to the spread of influenza are protected. Given that the overall seroprotection rate is estimated at 46% and 70% in school-age children, "these findings reassure against the likelihood of a substantial third pandemic H1N1 wave during the 2010-11 season, unless there is a significant waning of antibody or change in the virus" the authors state.

"Adults 50-79 years exhibited the lowest seroprotection and also remain at higher risk of severe outcomes if infected," they caution. "Our findings support a shift from the prioritized immunization of the young that occurred in fall 2009 to prioritized immunization of older adults for the coming 2010-11 influenza season to protect against severe outcomes due to both pandemic and seasonal influenza."

Attack on *C. difficile*: How can we combat this serious health issue
In five different studies presented at the American College of Gastroenterology’s (ACG) 75th Annual Scientific meeting in San Antonio, researchers explored the impact of various factors on increasing rates of *Clostridium difficile* infection (*C. difficile*), such as the use of proton pump inhibitors (PPIs) and the substantial increase in antibiotic use due to new National Hospital Quality Measures; strategies to combat high rates of *C. difficile* infections; and cutting-edge treatments for this potentially deadly—and quite common—infecction.

Five studies were featured during an ACG press briefing on Tuesday, October 18, 2010 entitled: "Attack on *C. difficile*: A GI Perspective - How We Can Combat this Serious Health Issue."

*C. difficile* associated diarrhea (CDAD) is a major cause of morbidity and increasing health care costs among hospitalized patients, as *C. difficile* infections have dramatically increased in recent years, with 500,000 cases in the United States annually and approximately 15,000 deaths each year, according to the U.S. Centers for Disease Control & Prevention.

**Proton Pump Inhibitors Linked to Incidence of *C. difficile* Associated Diarrhea**
While antibiotic use is the most documented risk factor for CDAD, attention has been directed towards a plausible--but controversial--link with proton pump inhibitors (PPIs). Researchers today unveiled results
of a meta-analysis of 16 observational studies, which explored the association between CDAD and PPIs. The study, "A Meta-analysis of 16 Observational Studies on Proton-Pump Inhibitor Use and Risk of Clostridium difficile Associated Diarrhea" investigated the association between PPIs and CDAD from 1980-2010 and involved more than 1.2 million hospitalized patients.

The investigators extracted adjusted risk estimates from the studies and used a random effects meta-analysis. The summary risk estimate showed a 65 percent increase in the incidence of CDAD among PPI users, according to Sailajah Janarthanan, M.D., who co-authored the study. Researchers also conducted a stratified analysis by study design and when looking at both prospective and retrospective studies, found that there was still a significant increase in C. difficile among PPI users.

**The Introduction of National Hospital Quality Measures Linked to Rising C. difficile Rates**

In 2004, the Joint Commission on Accreditation of Health Care Organizations (JCAHO) and the Centers for Medicare and Medicaid Services (CMS) introduced National Hospital Quality Measures (NHQM) to improve pneumonia and surgical infection outcomes. However, these new quality measures have resulted in a substantial increase of antibiotic usage, which researchers hypothesized has led to an increase in C. difficile associated diarrhea and colitis in an inner city hospital in New York. As a result, researchers reviewed charts of all patients with confirmed C. difficile infection admitted to the Bronx Lebanon Hospital Center from January 1, 2003 to December 31, 2008. Antibiotic usage for all inpatients during the same time was also reviewed.

The study, "National Quality Measures and Clostridium difficile Infection in an Inner City Hospital," found a total of 439 patients with confirmed C. difficile infection from January 1, 2003 to December 31, 2008.

"We observed significant increase in Clostridium difficile infection rate between 2003 and 2006," said Ariyo Ihimoyan, M.D. The number of cases per 10,000 admissions was 16 in 2003; 20 in 2004; 50 in 2005; 36 in 2006; 40 in 2007; and 58 in 2008. The total number of antibiotic doses uses per 1000 admissions was 3268 in 2003; 3536 in 2004; 4585 in 2005; 5150 in 2006; 5848 in 2007; and 5867 in 2008.

"From these findings, we conclude that the introduction of National Hospital Quality Measures have led to a substantial increase in antibiotic usage," said Dr. Ihimoyan. "We believe this resulted in an increase in Clostridium difficile infections in our patient population. Antibiotic usage-related quality measures may have resulted in unintended complications and should be re-evaluated."

**How Can We Combat C. difficile?**

Another study unveiled during the October 18 press briefing addressed the ways hospitals, gastroenterologists and other health care practitioners could combat C. difficile entitled, "Aggressive Attack on C. difficile Results in Significant Decrease in Hospital Infection Rate: the INTEGRIS Baptist Medical Center Experience."

Waging "an all out war on C. difficile," researchers implemented a number of measures over a three-month period at INTEGRIS Baptist Medical Center, a tertiary care facility in Oklahoma City which admits approximately 26,000 patients per year and experienced an increase in C. difficile cases.

"Aimed at reducing the incidences of C. difficile infections, these measures consisted of a multi-faceted attack on C. difficile, including improved prevention, early detection, review and full implementation of national infection control guidelines, and aggressive treatment measures," explained Mark H. Mellow, M.D., FACG, Center for Digestive Health, Oklahoma City, OK. "In addition to standard isolation procedures, we also elicited suggestions from physicians and nurses to best ensure compliance, such as placing a trashcan near the door to avoid traversing the room after de-gowning; keeping an uncluttered sink area; using appropriate size gloves; and making stethoscopes easily accessible," said Dr. Mellow.

Dr. Mellow and his team also initiated a campaign to limit proton pump inhibitor use outside of critical care units and encouraged nursing staff to send stool for C. difficile toxin (CDT) testing if C. difficile was suspected, without waiting for physician order.

"In the 12 months prior to our interventions, the incidence of CDT positive hospitalized patients was 11.3 per 100 admissions," said Dr. Mellow. "After a 3-month implementation period, the ensuing 12-month positive CDT incidence fell to 6.9 per 1000 patients, a decrease in C. difficile infection incidence of 40 percent. As a result, a 'war on C. difficile' can have a significant positive impact on a hospital's rate of infection," said Dr. Mellow.
Cutting Edge Treatments Help Patients with *C. difficile*

Up to 25 percent of patients will have a recurrence of *C. difficile* infection, and a proportion will be refractory to antibiotics. Additional therapies for this difficult-to-treat subpopulation include antibiotics, probiotics, toxin-binding medications, active vaccination, intravenous immunoglobulin, and fecal bacteriotherapy (FB).

"Fecal bacteriotherapy, more commonly known as fecal transplant, has been slowly gaining ground as a rescue for recurrent and refractory cases of *C. difficile* associated diarrhea," said C. Brock Miller, M.D., University of North Carolina at Chapel. Dr. Miller and his research team today reported findings from their initial experience using FB via colonoscopy, "Fecal Bacteriotherapy via Colonoscopy for Refractory and Recurrent *Clostridium difficile* Associated Diarrhea," which showcased two patients.

The first patient, a healthy 34-year old woman who developed CDAD after eight courses of antibiotics over six months, and had ongoing recurrences of CDAD, had an immediate improvement in symptoms and has been infection-free for nine months after fresh stool donated from her healthy 40-year old sister was liquefied and delivered throughout the terminal ileum and entire colon via colonoscopy.

A second patient, a healthy 50-year old female, who also developed recurrent *C. difficile* toxin positive diarrhea, elected to undergo FB via colonoscopy after testing and donation by her husband. She has been cured of *C. difficile* associated diarrhea to date, according to Dr. Miller.

"While further clinical studies and long-term follow-up of patients are required, fecal bacteriotherapy appears to be a viable, safe, and inexpensive option for cases of recurrent and refractory disease," said Dr. Miller.

The goal of another study unveiled today was to explore novel and inexpensive antimicrobial agents commonly found in nature in an effort to combat *C. difficile* in hospitals.

"For more than 2000 years in the Indian subcontinent, indigenous people have been using turmeric in their daily food," explained Rattan Patel, M.D. "Traditional Indian medicine, Ayurveda, has been using this spice to help decrease the rate of gastrointestinal infection."

In the study, "Inhibiting Hospital Associated Infection of Toxigenic *Clostridium difficile* Using Natural Spice – Turmeric (Curcumin)," Dr. Patel and his research team found that all strains of *C. difficile* were inhibited by turmeric extract (curcumin).

"Turmeric has been shown to be relatively safe in clinical studies, with more than 40 clinical trials already performed in the United States using curcumin as an intervention as per the Clinical Trail database," said Dr. Patel. "It's likely that daily use of turmeric in hospital settings, in food products like curry or soup, can potentially decrease the incidence of *Clostridium difficile* associated diarrhea. But more studies are needed to determine the mechanism of action of turmeric and the physiological effects of turmeric in animal models of pseudomembranous colitis," said Dr. Patel.

Mystery Solved: How Genes Are Selectively Silenced ****

ScienceDaily (Oct. 18, 2010) — Our genetic material is often compared to a book. However, it is not so much like a novel to be read in one piece, but rather like a cookbook. The cell reads only those recipes which are to be cooked at the moment. The recipes are the genes; 'reading' in the book of the cell means creating RNA copies of individual genes, which will then be translated into proteins.

The cell uses highly complex, sophisticated regulatory mechanisms to make sure that not all genes are read at the same time. Particular gene switches need to be activated and, in addition, there are particular chemical labels in the DNA determining which genes are transcribed into RNA and which others will be inaccessible, i.e. where the book literally remains closed. The biological term for this is epigenetic gene regulation.

Among the epigenetic mechanisms which are well studied is the silencing of genes by methyl groups. This is done by specialized enzymes called methyltransferases which attach methyl labels to particular 'letters' of a gene whereby access to the whole gene is blocked. "One of the great mysteries of modern molecular biology is: How do methyltransferases know where to attach their labels in order to selectively inactivate an individual gene?" says Professor Ingrid Grummt of the German Cancer Research Center (DKFZ).

Grummt has now come much closer towards unraveling this mystery. She has focused on studying those text passages in the genetic material which do not contain any recipes. Nevertheless, these texts are transcribed into RNA molecules in a controlled manner. "These so-called noncoding RNAs do not contain recipes for proteins. They are important regulators in the cell which we are just beginning to understand," says Ingrid Grummt.
In her most recent work, Grummt and her co-workers have shown for the first time that epigenetic regulation and regulation by noncoding RNAs interact. The scientists artificially introduced a noncoding RNA molecule called pRNA into cells. As a result, methyl labels are attached to a particular gene switch so that the genes behind it are not read. The trick is that pRNA exactly matches (is complementary to) the DNA sequence of this gene switch. The investigators found out that pRNA forms a kind of plait, or triple helix, with the two DNA strands in the area of this gene switch. Methyltransferases, in turn, are able to specifically dock to this 'plait' and are thus directed exactly to the place where a gene is to be blocked. More than half of our genetic material is transcribed into noncoding RNA. This prompts Ingrid Grummt to speculate: "It is very well possible that there are exactly matching noncoding RNA molecules for all genes that are temporarily silenced. This would explain how such a large number of genes can be selectively turned on and off."

Journal Reference:

October 18, 2010

Protecting Industry From the Consumer's Right-to-Know

The Return of Mad Cow Disease? ***

By MARTHA ROSENBERG

It’s been two years since rumors of mad cows in Texas sank cattle futures at the Chicago Mercantile Exchange when a woman with Creutzfeldt-Jakob Disease (CJD), human mad cow disease, was admitted to an Amarillo hospital.

"The rumor was started, and it's totally unfounded, that there were cattle with BSE in Texas," Ted McCollum, beef cattle specialist with the Amarillo office of Texas AgriLife Extension, told the press.

Of course it's easy to see how the rumor got started that there were cattle with BSE in Texas since there were cattle with BSE in Texas.

In 2005, the first "home grown" mad cow was found on a Texas ranch whose identity authorities protected. A 12-year-old beef cow used for breeding, she was sent to Champion Pet Food in Waco when she became a downer. The ranch was quarantined while authorities searched for the animal's offspring and older animals.

Now there are two "mysterious" cases of CJD in McLennan county, Texas says the Waco Tribune-Herald —"a statistical anomaly considering that only one in 1 million people worldwide is affected by the condition in any given year."

The statistical abnormality is also visible on the Texas Department of State Health Services map on its web site. There have been 144 cases of CJD in Texas since 2000 and 42 of them appear in clusters. If CJD is caused for unknown reasons (sporadic) or is familial, it would not come in clusters.

It has been years since the San Francisco Chronicle reported that 11 restaurants in nine California counties served meat from the first US mad cow, imported from Canada in 2003. A subsequent audit of US slaughterhouses to win back Asian exports which were lost over the cow, found 29 more downers slipped into the food supply because some inspectors "did not believe that they had the authority" to go into their pens. But then Secretary Johanns assured the press the cattle were healthy when they arrived at the slaughterhouse but became suddenly unable to walk for one reason or another.

Authorities also gave up tracing origins of the second homegrown US mad cow, born on an Alabama ranch, whose identity authorities also protected. The trail went cold after seven weeks of investigation of more than three dozen farms, said news reports.

In addition to food risks, unacknowledged mad cow in US beef could also be a risk in dental implants, made from bovine and cadaver sources.

And now there is also a cloud over deer and elk which get a mad cow like disease called chronic wasting disease (CWD). Like mad cow, CWD is caused by a practically indestructible protein called a prion which is not killed by cooking, alcohol, bleach, formaldehyde or radiation.

State Departments of Natural Resources thought the disease was under control after directing hunters to kill "antlerless" deer instead of bucks, thinning the herd. Food pantries were beginning to accept venison "donations" again after refusing them. ("It's perfectly good meat—for someone else to eat," the hunters seemed to be saying.)

But now the disease is back with a vengeance, causing hunters to fear the other guy's deer at the processor if not their own, until CWD tests come back, and wives to fear husbands' bloody laundry.
Prions are transmitted in carrier animals' urine and in antler velvet says a January article on PLoS One. Worse, they are likely transmitted from mother to offspring says the article, making US authorities' failure to find the mad cow progeny—and their progeny—more disquieting.

CWD is also taking a toll on deer breeding and hunting lodges, a $4 billion a year industry despite state complaints of deer "overpopulation." Wisconsin alone has hundreds of state sanctioned deer breeding farms.

Earlier this year, a deer with CWD was found at Heartland Wildlife Ranches in Ethel, Mo., 200 miles northwest of St. Louis. Heartland is an 800-acre lodge surrounded by 8-foot fences where hunters "come from across the country to take aim at trophy animals such as whitetail deer, elk and zebra," says the St. Louis Post-Dispatch. Think Dick Cheney. A three-day hunt for water buffalo costs $4,000.

In addition to threatening Rob Brasher of Salt Lake City, whose family has owned Heartland for two decades, CWD threatens David Wood, who runs the Linn County deer farm 17 miles from Heartland and can no longer sell his "baby deer" for $4,000 to $8,000.

Luckily, federal and state governments are on the mad cow and CWD case—protecting industry from consumers' rights to know.

**NeurogesX to Pursue Expanded U.S. Label for Qutenza® (capsaicin) 8% Patch in HIV-Associated Neuropathy**

**Targeting Supplemental New Drug Application in 1H 2011**

SAN MATEO, Calif., Oct. 18 /PRNewswire-FirstCall/—NeurogesX, Inc. (Nasdaq: NGSX), a biopharmaceutical company focused on developing and commercializing novel pain management therapies, today announced plans to pursue a U.S. label expansion for Qutenza® (capsaicin) 8% patch to include patients with painful HIV-associated neuropathy (HIV-AN, also referred to as HIV-distal sensory polyneuropathy (HIV-DSP)).

Following a recent meeting with the U.S. Food and Drug Administration (FDA), NeurogesX plans to submit a supplemental new drug application (sNDA) in the first half of 2011. The submission will utilize data from two completed Phase 3 studies in patients with HIV-AN.

Anthony DiTonno, President and CEO, commented, "As a company, we are focused on addressing unmet medical needs in pain and have made significant progress towards this goal with the U.S. launch of Qutenza. Our decision to submit a supplemental NDA to address the HIV-AN patient population is important as there are currently no FDA approved treatments for HIV-AN. U.S. label expansion to include HIV-AN would reach a new segment of neuropathic pain patients while leveraging our U.S. sales force and their relationships with pain specialists."

Qutenza is currently indicated in the U.S. for the management of neuropathic pain associated with postherpetic neuralgia (PHN), and has been evaluated in two Phase 3 studies in patients with HIV-AN. The FDA has previously granted orphan drug designation for the use of capsaicin to treat painful HIV-AN and fast track designation for Qutenza for the treatment of painful HIV-AN.

HIV-AN is thought to be caused by multiple factors related to HIV infection including injury of sensory neurons by HIV virus proteins; the immune system's fight against HIV; and some antiretroviral drugs. HIV-AN is the most common neurological complication of HIV infection, and many of these patients are afflicted with symptoms ranging from mild tingling to severe and excruciating pain.

**About NeurogesX, Inc.**

NeurogesX, Inc. (Nasdaq: NGSX) is a San Francisco Bay Area-based biopharmaceutical company focused on developing and commercializing novel pain management therapies. NeurogesX was founded on the concept that use of prescription-strength capsaicin could help manage the pain associated with neuropathic pain conditions. Since its inception, NeurogesX has leveraged its passion to help people with pain to efficiently develop this concept, resulting in the commercial launch of Qutenza® (capsaicin) 8% patch in 2010. The Company continues to apply its knowledge and expertise in the development of other novel treatments for pain.

The Company's lead product, Qutenza, is a localized dermal delivery system containing prescription strength capsaicin that is currently approved in the United States and the European Union. Qutenza is now available in the United States for the management of neuropathic pain associated with postherpetic neuralgia (PHN). In Europe, Qutenza is being marketed by Astellas Pharma Europe Ltd. (Astellas), the European subsidiary of Tokyo-based Astellas Pharma Inc., for the treatment of peripheral neuropathic pain in non-diabetic adults, either alone or in combination with other medicinal products for pain.
The Company’s most advanced product candidate, NGX-1998, is a topically applied liquid formulation containing a high concentration of capsaicin designed to treat pain associated with neuropathic pain conditions such as PHN. NGX-1998 has completed three Phase 1 studies.

The Company’s early-stage product pipeline includes pre-clinical compounds which are prodrugs of acetaminophen and various opioids. The Company has evaluated these compounds in vitro and in vivo.

Fed OKs Vivitrol to Treat Heroin, Narcotic Addictions

*USA Today*, (10.13.2010) Rita Rubin

A treatment already in use to treat alcoholism has been approved by the Food and Drug Administration to fight addiction to heroin and prescription narcotic painkillers.

Vivitrol offers several advantages over the opioids, methadone, and buprenorphine, typically used to treat narcotic addiction. It is delivered by monthly injection, not taken daily by mouth, so treatment adherence is easier.

Some believe that because Vivitrol itself is not an opioid, but a long-acting form of the opioid-blocking naltrexone, it may be more widely acceptable. “There are treatment programs that really oppose using methadone or buprenorphine,” said Nora Volkow, director of the National Institute on Drug Abuse (NIDA).

Vivitrol lists for $1,100 per shot, and since its 2006 approval as a treatment for alcoholism has been used by more than 45,000 people, according to Alkermes, the Waltham, Mass. manufacturer of the drug.

Few doctors, however, have taken advantage of the opportunity to use Vivitrol off-label to treat opioid addiction, Alkermes CEO Richard Pops said. “This is such a new market,” he said.

NIDA estimates that 810,000 Americans are addicted to heroin and 1.85 million are addicted to opioid painkillers such as OxyContin.

FDA’s expanded approval of Vivitrol was based on the strength of a study of 250 patients in Russia. Vivitrol was successful in keeping 70 percent of users, twice the success rate of a placebo, from returning to narcotics after six monthly shots. “I was concerned that the patients would not go back for their monthly injections, but they did, which was surprising,” Volkow said. She also was surprised that Vivitrol reduced cravings for narcotics.

Russia has rejected the use of methadone or buprenorphine, and heroin injection is a “major driver” of its HIV epidemic, Volkow said.

Ten Years Fighting HIV/AIDS and Reaching Out to Gays

*Inter Press Service*, (10.12.2010) Dalia Acosta

When a Cuban project to prevent HIV among men who have sex with men began 10 years ago, it was breaking new territory. MSM in Cuba were socially marginalized at the time of its first HIV/AIDS diagnosis in 1986, and the island’s compulsory quarantine of those infected lasted into the early 1990s. Among other challenges, reaching MSM required overcoming years of state-sponsored homophobia.

“Although homosexuality had been mentioned before, up to that point no work had been done with men,” said Raúl Regueiro, co-founder of the MSM-Cuba program.

“It was the first time the people most affected by HIV/AIDS participated in a program that was focused on educating people and on other aspects as well,” said Regueiro, who works with the UN Development Program on HIV in Cuba. “By using peer education as a tool, [MSM] themselves urged each other to practice safe sex.”

Of Cuba’s 13,000 recorded HIV cases, eight in 10 are men. Of these men, over 80 percent are MSM, including 60 percent who are bisexual.

Today, the national MSM-Cuba program has 1,700 volunteer outreach workers in 14 provinces. It also has contributed significantly to research on sexual minorities. A 2006 study estimated the project had prevented about 3,000 infections among men. Though the rate of consistent condom use was still below 75 percent in 2003, studies in 2006 and 2009 found an increase in MSM’s condom use with regular and casual partners. In addition, researchers are seeing a trend toward MSM living with stable partners.

Smoking-Related Health Risks Among Persons with HIV in the Strategies for Management of Antiretroviral Therapy Clinical Trial

*American Journal of Public Health Vol. 100; No. 10: P. 1896-1903*, (10.2010) Alan R. Lifson, MD, MPH; Jacqueline Neuhaus, MS; Jose Ramon Arribas, MD; Mary van den Berg-Wolf, MD; Ann M. Labriola, MD; Timothy R.H. Read, MBBS; and the INSIGHT SMART Study Group
Smoking prevalence is higher among HIV-positive persons than among the general population. In the current study, the researchers sought to determine smoking-related hazard ratios (HRs) and population-attributable risk (PAR) percentage for serious clinical events and death among HIV-positive persons.

For 5,472 HIV-positive persons enrolled from 33 countries in the Strategies for Management of Antiretroviral Therapy (SMART) clinical trial, the team evaluated the relationship between baseline smoking status, development of AIDS-related or serious non-AIDS events, and overall mortality.

Among participants, 40.5 percent were current smokers and 24.8 percent were former smokers. Compared to never smokers, adjusted HRs for current smokers were higher for overall mortality (2.4; P<.001), major cardiovascular disease (2.0; P=.002), non-AIDS cancer (1.8; P=.008) and bacterial pneumonia (2.3; P<.001). Compared to former smokers, current smokers also had higher adjusted HRs for these outcomes.

“The PAR percentage for current versus former and never smokers combined was 24.3 percent for overall mortality, 25.3 percent for major cardiovascular disease, 30.6 percent for non-AIDS cancer, and 25.4 percent for bacterial pneumonia,” the authors concluded. “Smoking contributes to substantial morbidity and mortality in this HIV-infected population. Providers should routinely integrate smoking cessation programs into HIV health care.”

Connecting Discovery and Delivery: The Need for More Evidence on Effective Smoking Cessation Strategies for People Living with HIV/AIDS

American Journal of Public Health Vol. 100; No. 7: P. 1245-1249, (07..2010) Jenine K. Harris, PhD

Compared to the general population’s smoking rate of 19.8 percent, smoking prevalence among people with HIV/AIDS is two to three times higher. The author of the current study cited discovery research showing that smokers with HIV/AIDS are more likely “to be nonadherent to treatment, have a greater chance of being diagnosed with an AIDS-defining condition or dying, and report lower quality of life” than nonsmokers with HIV/AIDS. She cited a recent study showing that 86 percent of smokers with HIV/AIDS would not benefit from standard smoking cessation programs.

Using the online database Web of Science, the author identified 1,532 articles with keywords related to smoking and HIV/AIDS published from 1980 through 2008. After those with no relevance were excluded, the remaining ones were classified as discovery, delivery or review.

“The present study found a lack of delivery research on smoking among this population and a scarcity of connections between discovery and delivery research,” the author wrote. “Although there is still a need for additional discovery of health effects associated with smoking for persons living with HIV/AIDS, it is time to disseminate evidence related to delivery of effective cessation interventions for this population.”

“I have two recommendations to this end,” the author noted. “1) Researchers and practitioners in the HIV/AIDS field should increase their collaborations with tobacco control researchers and practitioners, who have experience in population-specific cessation programs, and 2) because most discovery researchers are likely working toward a delivery goal (i.e., facilitating the reduction of smoking among persons living with HIV/AIDS), discovery researchers should report their findings in the context of how their contribution might aid intervention development or implementation.”

“Increasing collaboration among discovery and delivery researchers and linkages between discovery and delivery literature may facilitate more efficient synthesis of new evidence across the field and a faster transition from discovery of health risks to delivery of effective interventions.”

Antiretroviral Therapy Did Not Reduce HIV Transmission within Serodiscordant Couples in China

SUMMARY: A study of more than 1900 serodiscordant heterosexual couples in China, did not find evidence that use of antiretroviral therapy (ART) lowers the likelihood of HIV transmission, according to a report in the October 1, 2010 Journal of Acquired Immune Deficiency Syndromes. This finding conflicts with those of several other studies showing that effective HIV treatment does reduce transmission risk.

By Liz Highleyman

Effective combination ART typically reduces HIV RNA in blood plasma to an undetectable level, which most experts think dramatically lowers the risk of passing on the virus.

Prophylactic antiretroviral therapy to lower a pregnant woman’s viral load prior to delivery is the standard approach for preventing mother-to-child transmission. Several studies have shown that treating the HIV positive partner in a serodiscordant couple reduces the risk of transmission (though most
research of this sort has only looked at stable heterosexual couples). The Partners in Prevention, study, for example, recently reported that ART reduced transmission between heterosexual partners by 92%. Researchers saw only 1 new infection of a person whose HIV positive partner was on ART, for a rate of 0.37 per 100 person-years.

In early 2008, the Swiss Federal Commission for HIV/AIDS sparked controversy when it issued a report stating that an HIV positive person on antiretroviral therapy with no other sexually transmitted diseases and completely suppressed viral load for at least 6 months essentially cannot transmit HIV through heterosexual contact.

A new study from China, however, has reached a contradictory conclusion. Researchers sought to estimate HIV incidence (new infections) and assess the behavioral, clinical, and quality-of-life risk factors associated with HIV transmission among serodiscordant couples from Henan Province.

The HIV positive partners were former paid plasma donors infected through unsafe medical procedures; 80% were receiving free antiretroviral treatment. Between January 2006 and December 2008, initially HIV negative spouses were tested for HIV every 6 months, for a median follow-up period of 2.8 years; those found to be infected were interviewed in person.

HIV risk factors besides sex with a spouse were uncommon: 7 participants reported extramarital sex (1 seroconverted), 1 reported injection drug use (did not seroconvert), and none reported sex between men.

**Results**

- A total of 84 seroconversions occurred among 1927 couples (4%), for a seroconversion rate of 1.71 per 100 person-years.

- Seroconversion rates increased over time.

- Factors significantly associated with higher risk of transmission included:
  - Not always using a condom: relative risk (RR) 8.42, or more than 8 times greater risk;
  - Having sex 4 or more times per month: RR 5.24;
  - Using the same ART regimen without drug switches during follow-up: RR 1.99, or about twice the risk;
  - Quality-of-life psychological domain score < 12: RR 2.33.

- HIV transmission was equally likely, however, regardless of whether the positive partner received ART or remained untreated (5% vs 3%, respectively, not a significant difference).

- There was also no association between HIV infection risk and the positive spouse's last recorded CD4 cell count.

Based on these findings, the study authors concluded, "Effective HIV prevention interventions targeting discordant couples should focus on sustaining health education, increasing psychosocial support services, and increasing medication adherence monitoring."

In an accompanying editorial, Myron Cohen from the University of North Carolina at Chapel Hill attempted to make sense of these unexpected findings.

"Several studies of discordant couples demonstrate dramatically reduced risk to the HIV-negative sexual partner when the infected person takes ART," he noted. "And some (but not all) population based studies suggest the potential for falling prevalence of HIV in communities where ART is broadly used. Under idealized conditions, where most HIV-infected people are tested and treated and suppressed for life, it is possible to formulate a mathematical model where we literally 'treat our way out of the epidemic'."

It is not clear why ART did not reduce the likelihood of HIV transmission in the present study, though poor adherence may play a role. Viral load was not reported, which would have shown whether treatment was actually effective.

But the main point, according to Cohen, is that the Chinese patients were receiving routine health care, rather than the special management often used in studies that have shown a large decrease in new infections—for example frequent visits, advanced laboratory monitoring, and unique health care resources not available to the population at large.
"[A]t the end of the day, the success of the 'test and treat' idea for a population rests on the ability of ART to produce durable reduction of HIV transmission from treated people to their sexual partners," he wrote. "The results from Wang et al in China demand a giant pause. Will ART suppress the transmission of HIV under 'real life' conditions? It would seem more than wise to try to answer this question before we fully deploy a 'Test and Treat strategy,' expecting to detect a benefit to the general population." 10/19/10

References

**Intestinal Enzyme Helps Maintain Population of Beneficial Bacteria**

ScienceDaily (Oct. 18, 2010) — An enzyme that keeps intestinal bacteria out of the bloodstream may also play an important role in maintaining the normal microbial population of the gastrointestinal system. Since the loss of beneficial bacteria that usually results from antibiotic therapy can sometimes lead to serious health problems, a treatment that maintains microbial levels could have significant benefits.

"Our mouse studies confirmed that giving this enzyme by mouth keeps the gut healthy, in terms of the microbes that usually live there," says Richard Hodin, MD, of the Massachusetts General Hospital (MGH) Department of Surgery, senior author of the report in the November issue of the journal *Gut*. "This could prevent infection with dangerous bacteria like Salmonella and C. difficile, which can occur when the normal bacterial population becomes depleted, and may lead to development of a supplement to maintain intestinal health whenever someone takes an antibiotic."

Virtually all higher animals maintain a population of microbes—primarily bacteria—in their digestive tracts. These organisms are not only harmless, they also benefit their host by helping with digestion, and their presence prevents the more pathogenic bacteria that may be present from proliferating. Because antibiotics kill all non-resistant bacteria, including those residing in the intestines, the usual balance of beneficial versus harmful microbes is destroyed, leading to problems ranging from diarrhea to infections with dangerous antibiotic-resistant organisms.

A 2008 study by members of Hodin’s team that investigated why intestinal bacteria and their toxins do not pass into the bloodstream found that intestinal alkaline phosphatase (IAP), an enzyme produced by the intestinal lining, blocks the activity of a toxic molecule found on many pathogenic bacteria. Because that study and findings by other groups showed that IAP acts against several bacterial toxins, the MGH researchers looked at whether the enzyme directly interacted with intestinal bacteria.

Studies of mice lacking the gene for IAP revealed that the animals had reduced levels of all intestinal bacteria and practically none of the common beneficial strains of E. coli. In fact, the most common E. coli strain would not grow if introduced into these knockout mice. But when the animals received oral doses of IAP, beneficial E. coli proliferated quickly after other microbial species were killed by antibiotics. Experiments with normal mice infected with an antibiotic-resistant Salmonella strain showed that IAP treatment significantly reduced Salmonella levels in the animals’ feces. Although only 20 percent of animals not treated with IAP survived, 70 percent of those receiving the enzyme were alive 7 days later.

"We believe that IAP rapidly restores E. coli and other beneficial bacteria after antibiotic treatment and that the higher numbers of these bacteria prevent colonization by Salmonella or other pathogens by competing for nutrients and attachment sites," says Mahdu Malo, PhD, MBBS, of MGH Surgery, corresponding and first author of the *Gut* paper. "We need to test this approach in larger animals before planning a human clinical trial, but this approach has the potential of solving a common, often serious health problem."

**Journal Reference:**

Gut Microbes Promote Cell Turnover by a Well-Known Pathway

ScienceDaily (Oct. 18, 2010) —
Microbes matter—perhaps more than anyone realizes—in basic biological development and, maybe, they could be a target for reducing cancer risks, according to University of Oregon researchers.

In a study of very basic biology of zebrafish, scientists in the UO Institute of Molecular Biology focused on the developing intestine during its early formation in the sterile environment of its eggshell through the exposure to natural colonizing bacteria after hatching.

What they found was eye opening, said Karen Guillemin, professor of biology: Resident microbes in the still-maturing intestine send messages that promote non-disease-related cell proliferation in the same Wnt [pronounced went] signaling pathway where genetic mutations have long been known to give rise to colorectal cancer. The findings appeared online ahead of regular publication in the Proceedings of the National Academy of Sciences.

The complex Wnt pathway in the gut already is considered the starting point for more than 70 percent of sporadic colorectal cancers. In the study, researchers used normal zebrafish and those harboring mutations in the Wnt pathway. They were reared under germ-free conditions and then exposed under laboratory conditions to specific microbes to define how microbial signals interact with the Wnt pathway to promote cell proliferation in the gut.

"We were able to show that microbial signals do feed into and enhance signaling in the Wnt pathway. They feed in at a point after the node where most cancer-promoting genetic mutations occur," Guillemin said. "What this says is that for anyone who is at risk for developing cancer because they have these mutations, it matters what microbes these mutations are associated with. These two pieces of information contribute in parallel and feed into the same pathway."

The findings, she said, add fodder in an emerging shift in cancer research to look at the impact of microbes and other infectious causes of the disease. "It may be that associated microbes play as significant a role in cancer risk as genetic mutations," she said. "We need to learn more about the contributions of microbial signaling to cell proliferation. Maybe you could intervene with a targeted therapy. Even if you can't fix a mutation you might manipulate the associated microbes to change the interaction and reduce unwanted cell proliferation."

Genetic research on zebrafish—a high-priority model organism for the National Institutes of Health, which supported the project—began at the UO in the early 1970s. Guillemin, who recently received an early career investigator-scholar award from the NIH Institute of Digestive and Kidney Diseases, is known for her studies in zebrafish on the role of good bacteria in the gastrointestinal tract.

Journal Reference:
S. E. Cheesman, J. T. Neal, E. Mittge, B. M. Seredick, K. Guillemin. Microbes and Health Sackler Colloquium: Epithelial cell proliferation in the developing zebrafish intestine is regulated by the Wnt pathway and microbial signaling via Myd88. Proceedings of the National Academy of Sciences, 2010; DOI: 10.1073/pnas.1000072107

Africa: Botswana Ex-President in Plea Over Homosexuals

Elias Mbaa
19 October 2010
Nairobi — Botswana’s former president Festus Mogae yesterday said African governments and leaders must not enact laws that criminalise homosexuality and sex work, warning that such legislation would inhibit the fight against HIV/AIDS.

Mr Mogae, who chairs a team dubbed 'Champions of an HIV-Free Generation' that comprise prominent African anti-Aids activists, told Zambian President Rupiah Banda at State House in Lusaka
that homosexuals and sex workers were part of society and they should not be stigmatised or discriminated.

Mr Mogae said he had written to some African Presidents, without mentioning names, who wanted to pass laws to criminalise homosexuality, advising them not to do so.

Mo Ibrahim Foundation
Festus Gontebanye Mogae former president of Botswana.

The former President, who explained that he is heterosexual, said in Botswana homosexuality was illegal but he had been engaging the government to repeal the law that criminalises homosexuality.

Due to his advocacy, Mr Mogae said "nobody has been prosecuted over the last three years" for being homosexual.

And President Banda, whose government is anti-gay rights, accused the foreign donors were making youths believe that "homosexuality is a human right and that if you appear to speak against it then you are a reactionary and you don't understand the world".

Without categorically backing Mr Mogae's position, President Banda said to "hear it from the position of the Champions in the fight against Aids then you understand why we should not criminalise them [homosexuals], understand them and at the same time try and sensitize our young people" about homosexuality.

Zambia: Criminalising HIV Transmission
20 October 2010
FORMER Botswana president Festus Mogae's suggestion that no country should pass laws that criminalise HIV transmission is likely to stir emotions among anti-AIDS campaigners, but his views need careful study.

In many countries, the intentional or reckless infection of a person with the human immunodeficiency virus (HIV) is considered to be a crime. People who do so can be charged with criminal transmission of HIV, murder, manslaughter, attempted murder, or assault.

Some reports indicate that some countries have enacted laws to criminalise HIV transmission, as in the United States, while others charge under the existing laws, as in the United Kingdom.

Mr Mogae, who is the chairperson of the Champions for an HIV Free Generation, joins the body of thinking that criminalising HIV transmission is not the answer to scaling down the pandemic.

Mo Ibrahim Foundation
Festus Gontebanye Mogae former president of Botswana.

There has been growing concern among policy makers and women's groups over the increasing number of women being infected with the virus through sexual violence or by partners who refuse to disclose their HIV status.

The general agreement is that such concerns are reasonable, and people who maliciously and purposefully infect others with the virus must be punished.

However, there are some experts who argue that the use of criminal law as a strategy to fight the pandemic risks increasing discrimination and stigma against people living with HIV.

The debates around HIV and AIDS are as delicate as they rouse firestorms, but it is important to treat views of any interest groups with objectivity for the common goal of creating an HIV-free generation.

Gays in Uganda say they're living in fear
Recent front-page newspaper headline proclaimed: 'Hang them'

By Godfrey Olukya, Jason Straziuso
KAMPALA, Uganda— The front-page newspaper story featured a list of Uganda’s 100 "top" homosexuals, with a bright yellow banner across it that read: "Hang Them." Alongside their photos were the men's names and addresses.

In the days since it was published, at least four gay Ugandans on the list have been attacked and many others are in hiding, according to rights activist Julian Onziema. One person named in the story had stones thrown at his house by neighbors.

A lawmaker in this conservative African country introduced a bill a year ago that would have imposed the death penalty for some homosexual acts and life in prison for others. An international uproar ensued, and the bill was quietly shelved. But gays in Uganda say they have faced a year of harassment and attacks since the bill's introduction.
The legislation was drawn up following a visit by leaders of U.S. conservative Christian ministries that promote therapy they say allows gays to become heterosexual. "Before the introduction of the bill in parliament most people did not mind about our activities. But since then, we are harassed

**Sterilizing with fluorescent lights**

**New surface may kill antibiotic-resistant staph bacteria with fluorescent light**

WASHINGTON, D.C., (Oct. 19, 2010)—The prevalence of methicillin-resistant Staphylococcus aureus (MRSA) infections is well known, causing an estimated 19,000 deaths and $3-4 billion in healthcare costs per year in the U.S. What is less well known is that this increased infection and resistance rate has not been met with a simultaneous development of novel antimicrobial and antibiotic agents; in fact, only three classes of antibiotics have been developed since the 1950s.

To address this need, scientists at the University of New Mexico are working on a new type of antimicrobial surface that is inhospitable to MRSA but won’t harm people or animals. Their results will be presented today at the AVS 57th International Symposium & Exhibition, which takes place this week at the Albuquerque Convention Center in New Mexico.

The new polymer-type material, "conjugated polyelectrolyte" (CPE) with an arylene-ethynylene repeat-unit structure, has been effective at killing Gram-negative bacteria, enabling its use in a wide range of potential applications. For instance, certain "light-activated" CPEs are inert toward bacteria in the absence of light, and display bacteria-killing activity with the addition of light. This opens up many potential applications, including the possibility of using these polymers as antibacterial countertops that may be sterilized using regular fluorescent lights.

Until recently, it was unknown if the CPEs would exhibit similar biocidal activity toward mammalian cells. In-vitro testing performed on these CPEs at the University of New Mexico is an important first step in determining whether they are harmful to humans at concentrations envisioned in potential applications. In a poster presented today at the AVS Conference, Kristin Wilde will present the results.

**No Standard for the Placebo?**

ScienceDaily (Oct. 19, 2010) — Much of medicine is based on what is considered the strongest possible evidence: The placebo-controlled trial. A paper published in the October 19 issue of *Annals of Internal Medicine*—entitled "What’s In Placebos: Who Knows?" calls into question this foundation upon which much of medicine rests, by showing that there is no standard behind the standard—no standard for the placebo.

The thinking behind relying on placebo-controlled trials is this: to be sure a treatment itself is effective, one needs to compare people whose only difference is whether or not they are taking the drug. Both groups should equally think they are on the drug—to protect against effects of factors like expectation. So study participants are allocated "randomly" to the drug or a "placebo"—a pill that might be mistaken for the active drug but is inert.

But, according to the paper’s author, Beatrice Golomb, MD, PhD, associate professor of medicine at the University of California, San Diego School of Medicine, this standard has a fundamental problem, "there isn’t anything actually known to be physiologically inert. On top of that, there are no regulations about what goes into placebos, and what is in them is often determined by the makers of the drug being studied, who have a vested interest in the outcome. And there has been no expectation that placebos’ composition be disclosed. At least then readers of the study might make up their own mind about whether the ingredients in the placebo might affect the interpretation of the study."

Golomb pointed out these limitations to the placebo in a pair of letters to the journal *Nature 15 years ago.*

"A positive or negative effect of the placebo can lead to the misleading appearance of a negative or positive effect of the drug," she said. "And an effect in the same direction as the drug can lead a true effect of the drug to be lost. These concerns aren’t just theoretical. Where the composition has been disclosed, the ingredients of the placebo have in some instances had a likely impact on the result of the study—in either direction (obscuring a real effect, or creating a spurious one). In the cases we know about, this is not because of any willful manipulation, but because it can in fact be difficult to come up with a placebo that does not have some kind of problem."

Since 15 years have elapsed, the situation might have improved. Therefore, Golomb and her colleagues analyzed just how often randomized trials published in the past two years in each of the top four general medical journals actually disclosed the makeup of placebos.
The answer is not reassuring, according to the researchers, who found that the placebo ingredients for pills were disclosed in fewer than 10 percent of cases. (The nature of the "control" was significantly more likely to be stated for other types of treatments—like injections, acupuncture, or surgery—where people are more likely to question what "placebo" actually means.)

"How often study results are affected by what's in the placebo is hard to say—because, as this study showed, most of the time we have no idea what the placebo is," Golomb concluded.

**Journal Reference:**

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**Improved Antibiotic Coatings: Research Aims to Make Medical Devices Safer by Preventing Biofilms**

ScienceDaily (Oct. 19, 2010) — Bacteria have a natural ability to attach themselves to surfaces, both natural and synthetic. Once attached, they often work cooperatively to form biofilms, thin layers of bacterial colonies that can coat the surface of a medical device and introduce the risk of infection. As a result, orthopedic implants, catheters, and even contact lenses can become vehicles for infection.

Antibacterial materials on the surface can reduce the risk but generally these materials do not stick well to the devices. A research group at the University of South Australia is working on techniques to permanently bind antibacterial coatings to medical devices by binding them to a polymer layer. They present their research at the AVS 57th International Symposium & Exhibition, which takes place this week at the Albuquerque Convention Center in New Mexico.

The Australian scientists start by applying a plasma polymer coating, a technique that works on many different base materials including glass, metal, and many polymers used in devices. This ultrathin film acts as a scaffold on which to bind materials that either signal the bacteria not to attach by interfering with the cell's attachment mechanism or that prevent multiplication once the bacteria are attached.

The presentation will compare several different antibiotics applied to the polymer film, including established antibiotic compounds, silver nanoparticles, and novel diterpene compounds derived from Australian plants that have been used in traditional medicine. Each approach has pros and cons that must be carefully weighed before using them on a device implanted in the human body.

"We believe that no solution will be universal so we want to establish an array of approaches," says Hans Griesser of the University of South Australia. "The new diterpene compounds that we are testing are structurally quite different from established antibacterial compounds, and they are effective against methicillin-resistant *Staphylococcus aureus*. That is what got us excited about them."

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**HIV transmitted during a knife attack**

Michael Carter
Published: 21 October 2010

Investigators in Taiwan have identified a case of HIV transmission due to a knife fight. The case is reported in the online edition of *AIDS Research and Human Retroviruses*. The researchers used phylogenetic analysis to link the virus in the attacker and victim, and they also argue that new HIV testing technology allowed them to determine the direction of HIV transmission.

Most cases of HIV infection have occurred as a consequence of unprotected anal or vaginal sex. However, the virus can also be spread through blood-to-blood, and there are reports of HIV being transmitted during fist fights.

Now investigators have found compelling evidence of HIV transmission from one individual to another during a knife attack.

The attack occurred in September 2008. The attacker was a 42 year old who had been diagnosed HIV-positive in December 2005. His CD4 cell count was 445 cells/mm³ and his viral load was 57,700 copies/ml. He was not taking antiretroviral therapy and had a history of injecting drug use.

He attempted to rob a 69-year-old man and in the ensuing fight both sustained serious injuries and were hospitalised. The victim received blood transfusions during surgery after the fight. He was married with children, and reported no history of injecting drug use or any other HIV risk behaviour. In October 2008 both he and his wife tested HIV-negative.

However, in February 2009 the victim, but not his wife, became HIV-positive.

His blood transfusion was ruled out as the mode of transmission as all the donors were HIV-negative. Therefore, investigators hypothesised that the individual’s infection was due to blood-to-blood contact during the knife attack.
To test this theory blood samples were obtained from both the attacker and the victim. Both individuals were infected with the same HIV subtype (HIV-1CRF07_BC). Phylogenetic analysis of both the env and pol regions also showed that the virus in the two individuals was very closely related.

The investigators also believe that they have proof of the direction of HIV transmission. Levels of HIV-IgG were measured in the two individuals. Levels of IgG increase with the duration of HIV infection. Levels of IgG increased in the victim and, write the investigators, “provided...the evidence for the direction of HIV-1 transmission from the robber to the victim.” They add, “we conclude that this HIV transmission most likely resulted from blood-to-blood contact during a fierce fight...it is the first case providing HIV-1 seroconversion data as evidence to establish the direction of HIV-1 transmission.”

Reference

Drug safety bodies issue warning on heart rhythm risks with saquinavir (Invirase)

Keith Alcorn
Published: 22 October 2010

The US Food and Drug Administration and the European Medicines Agency have strengthened their warnings to doctors and patients about the potential of the HIV protease inhibitor saquinavir (Invirase) to cause disturbances in electrical activity in the heart leading to abnormal heart rhythm when the drug is combined with a boosting dose of ritonavir (Norvir).

Saquinavir has been linked to prolonged QT and PR intervals in the heart’s electrical cycle in a study in healthy volunteers.

The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart’s electrical cycle. A prolonged QT interval is a risk factor for cardiac arrhythmias. The PR interval measures a phase of electrical activity that precedes the QT interval.

A prolonged QT interval can lead to a serious abnormal rhythm called torsades de pointes, which can be fatal. A prolonged PR interval can lead to a serious abnormal rhythm called complete heart block. Torsades de pointes and complete heart block have been reported in a very small number of patients taking saquinavir with ritonavir.

Although QT prolongation is likely to be a rare adverse event, the European Medicines Agency now recommends that every patient starting saquinavir should receive electrocardiogram monitoring prior to and after the start of treatment.

The US Food and Drug Administration makes a more detailed recommendation, saying that patients with a QT interval > 450 msec should not receive ritonavir-boosted Invirase. For patients with a QT interval < 450 msec, an on-treatment ECG is suggested after approximately 3 to 4 days of therapy. Patients with a QT interval > 480 msec or with prolongation over pre-treatment by > 20 msec should discontinue saquinavir/ritonavir.

The FDA recommends to anyone taking saquinavir: “Seek immediate care if you experience an abnormal heart rate or rhythm or other symptoms including dizziness, lightheadedness, fainting or heart palpitations.”

The European Medicines Agency also recommend that the dosage of saquinavir for the first week of treatment will be reduced from 1000 mg twice daily to 500 mg twice daily for treatment-naïve patients initiating therapy with saquinavir/ritonavir. The agency says that this dosage adjustment is designed to minimise cardiac risk during the time that the risk is thought to be highest.

This dosage adjustment is not necessary in patients who are switching from other antiretroviral drugs; the European Medicines Agency says the risk of QT prolongation is greatest in people who have never taken antiretroviral drugs before.

The US Food and Drug Administration has made no recommendation regarding dosage adjustment. Saquinavir’s manufacturer Roche is also planning to conduct a new clinical study to investigate the potential risk of arrhythmia in treatment-naïve patients receiving the reduced starting dose of Invirase in combination with other antiretroviral medications.
SOUTH AFRICA: Research shows World Cup did not fuel sex work or HIV

JOHANNESBURG, 22 October 2010 (PlusNews)—The South African sex work industry has released a new report that has shown the country’s recent soccer World Cup did not fuel a rise in sex work—and that thousands of dollars may have been wasted on ill-tailored HIV prevention campaigns.

New research by the South Africa’s Sex Workers Education and Advocacy Taskforce (SWEAT) and partners such as the UN Population Fund (UNFPA) has shown that sex work was unlikely to have fuelled any rise in HIV infections during South Africa’s recent month-long World Cup, contrary to expectations.

The first study to examine the affects of a soccer World Cup on the sex trade in a host country, the research surveyed female sex workers who advertised their services in print or online and found that while slightly more sex workers were advertising, these women reported no significant increase in clients. Reported condom use among respondents was about 99 percent, according to the research.

SWEAT also announced that it found no evidence of human trafficking, supporting similar claims by the South African Department of Justice, and that the proportion of non-South African sex workers advertising actually dropped.

In the months leading up to the World Cup, what SWEAT called “media sensationalism” predicted as many as 100,000 sex workers would flood South Africa to cater to visiting tourists, and that unsafe sex among sex workers and clients could fuel a rise in HIV infections. In particular, predictions were made that women and children would be trafficked into the host cities as part of the sex trade, and that the country—with an HIV prevalence rate of about 19 percent—would experience condom shortages.

For its part, SWEAT increased its own safe-sex campaigns almost threefold during the World Cup through a massive distribution of male and female condoms, and safer sex workshops and the establishment of a telephone help-line for sex workers.

Lots of money, wrong direction

But according to a statement released by SWEAT and UNFPA, the research findings may mean public fears, not evidence, drove many of the HIV-prevention programmes aimed at sex workers and potential clients during the month-long international event.

“In response to this media frenzy and public fears, a number of national and international health, gender and development agencies invested substantial funds in the distribution of free male condoms, generalized HIV/AIDS information campaigns for South Africans and visitors, and rolling out anti-trafficking campaigns,” said the statement. “Yet, none of these investments were based on rigorous research or inquiry and could have been better employed if done in a targeted manner.”

Head researcher Marlise Richter told IRIN/PlusNews the money spent on this kind of programming could have been better allocated towards protecting sex workers from increased human rights abuses during the Cup, such as harassment, violence and sexual bribery at the hands of law enforcement officers.

The organizations, who also critiqued the lack of female condom distribution as part of World Cup HIV prevention measures, said they hoped the research would help inform future HIV programming around international events like the 2010 World Cup.

“Future campaigns and programmes that focus on sex work, trafficking and international sporting events should be based on systematic research—not sensationalism that leads to further stigmatization and discrimination against sex workers while increasing their vulnerability to violence,” said the organizations in a written statement.

SWEAT is due to release a follow-up report in Johannesburg at the end of November that examines the World Cup’s affects on street-based sex work.

FDA Warns of Heart Risk with HIV Drug Combination

Associated Press, (10.21.2010)

The Food and Drug Administration on Thursday announced that Invirase (saquinavir) labeling has been changed to warn of potentially life-threatening heart rhythm abnormalities when the HIV drug is used in combination with Norvir (ritonavir). In February, FDA warned patients and health care providers about this possibility.

When taken together, the two drugs can cause prolongation of the QT and PR intervals—indicators of heart rhythm activity seen on an electrocardiogram. “Patients at particular risk are those with underlying heart conditions or those who have existing heart rate or rhythm problems,” FDA said.

“Prolongation of the QT interval may lead to a condition known as torsades de pointes, an abnormal heart rhythm,” the FDA notice said. “With torsades de pointes, patients may experience lightheadedness,
fainting or abnormal heart beats. In some cases, torsades de pointes may progress to a life-threatening irregular heart beat known as ventricular fibrillation.”

“Prolongation of the PR interval may also lead to an abnormal heart rhythm known as heart block,” the advisory said. “With heart block, patients may experience lightheadedness, fainting or abnormal heart beats.”

FDA also is requiring a medication guide for patients using Invirase that will describe these risks. The agency advises patients not to discontinue Invirase without talking to their health care professional.

“Patients should talk to their doctor if they have any concerns about their treatment,” said Edward Cox, MD, MPH, director of the Office of Antimicrobial Products in FDA’s Center for Drug Evaluation and Research. “Certain drugs may interact with Invirase and increase the risk of developing these side effects, so patients should be sure to tell their doctor about other medicines they may be taking, including non-prescription medicines, vitamins, and herbal supplements.”

For more information, visit: http://www.fda.gov/Drugs/DrugSafety/ucm230096.htm.

Southern Africa Life Expectancy Rising Slightly: UN

A new UN report finds that an AIDS-related drop in life expectancy in southern Africa during the 1990s may have leveled out, though women in the region continue to be hardest-hit by the epidemic.

The report, “The World’s Women 2010,” finds that women comprise the majority of HIV-positive adults in sub-Saharan Africa, as well as in northern Africa and the Middle East. While antiretroviral treatment has brought about a slight rise to life expectancy in southern Africa in recent years, it remains the only region in the world where life expectancy today is lower than in the early 1990s, particularly for women.

From 1990 to 1995, life expectancy at birth in the region—composed of South Africa, Namibia, Botswana, Swaziland, and Lesotho—was 64 for women and 59 for men. By 2000-05, it had fallen to 51 for women and 49 for men. From 2005 to 2010, life expectancy rose slightly to 52 for women and 51 for men. The UN report attributes the increase to the improved availability of HIV treatment in the region.

In eastern, central, and western Africa, regions that also include countries hard-hit by HIV/AIDS, life expectancy has steadily increased over the same period and currently stands at 57 for women and 54 for men.

Sub-Saharan Africa is home to approximately two-thirds of all people living with HIV/AIDS worldwide. In South Africa, 5.7 million people are HIV-infected, and roughly 1,000 die every day from AIDS-related complications.

In all regions of the world, women live longer than men by an average of five years, the report found. The longest life expectancies were noted in Japan (86 for women) and Iceland (80 for men). Afghanistan and Zimbabwe have the lowest life expectancies: below 45 for men and women alike.

TB Cases Decline, but Drug-Resistant TB Now a Risk

Prevention and treatment efforts have been successful at driving down tuberculosis rates in the United States, but the nation now may be more vulnerable to multidrug-resistant TB (MDR TB), according to a new study.

Dr. David Bishai, of the Johns Hopkins Bloomberg School of Public Health, and colleagues used computer modeling “to determine the role of declining prevalence of drug-susceptible TB in enabling future epidemics of MDR TB.”

“Prior infection with one strain of TB has been linked with diminished likelihood of reinfection by a new strain,” the authors noted. The study’s results indicated that “MDR TB epidemics propagated more extensively after prevalence had fallen.

“At a case detection rate of 75 percent, improving therapeutic compliance from 50 percent to 75 percent can reduce the probability of an epidemic from 45 percent to 15 percent. Paradoxically, improving the case-detection rate from 50 percent to 75 percent when compliance with DOT [directly observed therapy] is constant at 75 percent increases the probability of MDR TB epidemics from 3 percent to 45 percent.

“The ability of MDR TB to spread depends on the prevalence of drug-susceptible TB,” the authors concluded. “Immunologic protection conferred by exposure to drug-susceptible TB can be a crucial factor that prevents MDR TB epidemics when TB treatment is poor. Any single population that successfully
reduces its burden of drug-susceptible TB will have reduced herd immunity to externally or internally introduced strains of MDR TB and can experience heightened vulnerability to an epidemic. Since countries with good TB control may be more vulnerable, their self interest dictates greater promotion of case detection and [directly observed therapy, short course] implementation in countries with poor control to control their risk of MDR TB."

Bishai added, “The most successful approach to reduce this risk for MDR TB epidemics in the United States would be to ensure that populations around the world combine high rates of case findings that are tightly coupled to high compliance with directly observed drug therapy.”


**Hepatitis C Virus Can Damage Brain Cells**

*Edmonton Journal*, (10.06.2010) Sarah O’Donnell

Hepatitis C virus (HCV) can damage not only the liver but also the brain, according to a new Canadian study.

“It has been a question for a long time,” said study co-author Pornpun Vivithanaporn, a post-doctoral fellow in the University of Alberta’s Faculty of Medicine and Dentistry. “It proves the virus has implications on neurological disease.”

The study showed HCV “gets in [the brain], it infects, and it replicates,” said lead author Dr. Christopher Power, a neurologist at the university. A buildup of HCV proteins in healthy brain cells eventually damages and kills the cells, as if the cells were drowning in their own refuse, he said.

“HCV core protein exposure caused neuronal injury through suppression of neuronal autophagy in addition to neuroimmune activation,” the study concluded. “The additive neurotoxic effects of HCV- and HIV-encoded proteins highlight extrahepatic mechanisms by which HCV infection worsens the disease course of HIV infection.”

Researchers already knew that severe liver damage can affect the patient’s brain. The new findings support other studies showing that even when serious liver damage has not occurred, HCV patients might develop memory loss, trouble concentrating, apathy, and depression.

“It tells us we need to be vigilant for neurological problems for people who have hepatitis C,” Power said. An HCV patient’s treatment team might need to include a neurologist and a psychologist, as well as the liver specialist, he said.

The study, “Hepatitis C Virus Core Protein Induces Neuroimmune Activation and Potentiates Human Immunodeficiency Virus-1 Neurotoxicity,” was published in Public Library of Science ONE (doi: 10.1371/journal.pone.0012856).

**Helena School Board OK’s Revised Sex Education Plan**


Helena school district trustees voted 6-3 on Oct. 12 in favor of a revised sex education curriculum.

School officials first proposed the plan last summer, but it was quickly withdrawn due to complaints that it was too graphic and too detailed. Under the new version, officials removed plans to teach first-graders that people of the same gender can love each other, and they ensured that from fifth grade, students will be taught that abstinence is the “healthy choice” and the “only 100 percent effective way” to prevent STDs and pregnancy.

But the changes are not enough for some religious and conservative parents who argue that sex education should be taught at home, not at school. “This is going to send people into isolation,” said school board member Trevor Wilkerson. His proposal to send the curriculum back to the planning stage and to highlight the sex education component for further scrutiny was rejected.

“It is going to divide our community. I don’t think it is the right curriculum for us,” Wilkerson said to loud cheers from opponents of the curriculum.

Other board members said the curriculum is needed now more than ever. “There is no dispute that kids learn about sex very early,” said trustee Donald Jones. “The facts they get from the media and their peers are skewed. Innocence cannot be a justification for ignorance.”

School Superintendent Bruce Messinger told trustees the revised plan “reflects the values and expectations of the Helena community and will provide quality, comprehensive health education for all students.” He plans to develop a specific curriculum that will be taught beginning next school year. Messinger will seek ongoing feedback from parent, teacher, and student advisory councils to ensure that no one feels left out of the process.
Study Uncovers Structure of CXCR4 Co-receptor Used by HIV to Enter Cells

SUMMARY: As described in the October 7, 2010 advance online edition of Science, researchers have determined the crystal structure of a chemokine receptor known as CXCR4 that enables certain strains of HIV to enter host cells including CD4 T-cells. Receptors of this type also play a role in regulating cell proliferation, and therefore can contribute to the development and spread of malignancies. Scientists hope this new insight will aid discovery of agents to control CXCR4 activity, possibly leading to new therapies for HIV and cancer.

Below is the text of a press release from the National Institutes of Health, which funded the study, describing the new findings.

Study Details Structure of Potential Target for HIV and Cancer Drugs

October 7, 2010—In a technical tour de force, structural biologists funded by the National Institutes of Health have determined the three-dimensional structure of a molecule involved in HIV infection and in many forms of cancer. The high-resolution structure sheds light on how the molecule functions and could point to ways to control its activity, potentially locking out HIV and stalling cancer's spread.

The molecule, CXCR4, is part of a large family of proteins called G-protein coupled receptors (GPCRs). These molecules span the cell's membrane and transmit signals from the external environment to the cell's interior. GPCRs help control practically every bodily process, including cell growth, hormone secretion and light perception. Nearly half of all drugs on the market target these receptors.

"Scientists have been studying CXCR4 for years but have only been able to guess at what it looks like," said NIH Director Francis S. Collins, MD, PhD. "Now that we have its structure, we have a much clearer picture of how this medically important molecule works, opening up entire new areas for drug discovery."

The researchers, led by Raymond C. Stevens, PhD, of the Scripps Research Institute in La Jolla, Calif., report their findings in the Oct. 7, 2010, advance online issue of the journal Science. The study received support from two major NIH initiatives: the structural biology program of the NIH Common Fund and the Protein Structure Initiative (PSI).

While a molecule called CD4 is the primary receptor for HIV, CD4 is not sufficient for the virus to penetrate cells. In 1996, a team of researchers at NIH's National Institute of Allergy and Infectious Diseases (NIAID) discovered that CXCR4 acts as a co-receptor by helping HIV enter cells.

Normally, CXCR4 helps activate the immune system and stimulate cell movement. But when the signals that activate the receptor aren't properly regulated, CXCR4 can spur the growth and spread of cancer cells. To date, CXCR4 has been linked to more than 20 types of cancer.

The Scripps Research scientists set out to shed light on how CXCR4 functions by capturing snapshots of the protein by using a structure determination method called X-ray crystallography. To understand how natural molecules might bind and signal through the receptor and to see how potential drugs could interact with it, they examined CXCR4 bound to known inhibitors of its activity.
Determining the structure of CXCR4 represented a major challenge because membrane proteins are notoriously tricky to coax into the crystal form required for the X-ray technique. After three years of optimizing conditions for producing, stabilizing and crystallizing the molecule, the scientists finally generated five distinct structures of CXCR4.

The structures showed that CXCR4 molecules form closely linked pairs, confirming data from other experiments indicating that pairing plays a role in the proper functioning of the receptor. With this knowledge, scientists can delve into how the duos might regulate CXCR4's activity and better understand how CXCR4 functions under normal and disease conditions.

The images also showed that CXCR4 is shaped like two white wine glasses touching in a toast, with the inhibitors bound at the sides of the bowls. By detailing these contacts, the researchers said the pictures suggest how to design compounds that regulate CXCR4 activity or block HIV entry into cells. If developed into drugs, such compounds could offer new ways to treat HIV infection or cancer.

"An approach to determining protein structures that was developed with support from the NIH Common Fund and the PSI is now paying huge dividends," said Jeremy M. Berg, PhD, director of the National Institute of General Medical Sciences, which supports the PSI. "It illustrates how technical progress provides a foundation for rapid advances, and it also showcases the benefits of collaborations between structural biologists and scientists working in other fields for addressing fundamentally important problems with tremendous potential for medical applications."

Reference

**Phase 2 Trial Tests Intensified Antiretroviral Therapy plus Interleukin-7 for HIV Eradication**

**SUMMARY:** Biopharmaceutical company Cytheris announced this week that it has started a clinical trial to evaluate an intensive antiretroviral and immune-modulator regimen designed to reduce—and ideally eliminate—HIV in latently infected reservoir cells. Participants will intensify their current suppressive regimen by adding the 2 newest antiretroviral drug classes, along with interleukin 7 (IL-7) to activate resting CD4 T-cells.

**By Liz Highleyman**

The past year has seen renewed interest in curing HIV, either by completely eradicating the virus or lowering levels enough to enable a "functional cure" that allows HIV positive people to safely stop antiretroviral therapy (ART).

Researchers have debated whether residual virus in people on suppressive ART is due to continued low-level replication or to virus escaping from latent reservoirs such as resting CD4 cells or anatomic sites such as the brain.

To date, most studies have shown that intensifying treatment by adding more antiretroviral drugs is **not enough to eliminate HIV**. This has led researchers to ask whether a more potent and diverse intensification strategy combining antiretrovirals with immune-modulating agents might hold more promise.

In the EraMune trial, people with suppressed HIV on standard ART will add drugs from the 2 most recently approved antiretroviral classes—inTEGRase inhibitors and CCR5 antagonist entry inhibitors—plus IL-7 to activate resting cells. Investigators hope this approach will "flush out" the latent cell reservoir by triggering silent integrated proviral DNA to start producing new virus, which will then be susceptible to the potent antiretroviral drug combination.


**Cytheris Announces Initiation of ORVACS-Sponsored Phase II Clinical Study combining Immunomodulatory Intervention with Interleukin-7 (CYT107) and Antiretroviral Intensification with Raltegravir and Maraviroc to Attack the Viral Reservoir of HIV Patients**

*By combining an integrase inhibitor and a CCR5 inhibitor with IL-7 to target or induce activation of latently infected cells, study aims to investigate whether exhausting the HIV reservoir and ultimately obtaining virus eradication is feasible.*

Paris—October 19, 2010—Cytheris SA, a clinical stage biopharmaceutical company focused on research and development of new therapies for immune modulation, today announced the initiation of Phase II clinical trial of the company's investigative immunomodulatory agent, CYT107 (rhIL-7), in combination with two potent antiretroviral drugs represented by the integrase inhibitor raltegravir (Isentress—Merck
& Co.) and the CCR5 inhibitor, maraviroc (Selzentry—ViiV Healthcare). The main hypothesis of this study is that by combining the most potent and synergistic antiretroviral drugs, coupled with an immunomodulating agent capable of targeting or inducing activation of latently infected cells, the reservoirs of HIV can be decreased and, in the best case scenario, eradication of the virus may be feasible.

The trial, known as EraMune 01, is designed and sponsored by the French not-for-profit institution Objectif Recherche VACcin Sida (ORVACS) with financial support from the Bettencourt-Schueller Foundation, Paris, France. Since its creation in 2001, ORVACS, together with the support of its international network of excellence, has focused its resources and efforts, on the development of innovative immunotherapeutic and vaccine strategies against HIV. Under the direction of Prof. Christine Katlama, MD (Principal Investigator), Head of the AIDS Clinical Research Unit, Department of Infectious Diseases, Hopital Pitie-Salpetriere, Paris, France, and Bonaventura Clotet, MD, PhD (co-Principal Investigator), Chief of the Internal Medicine HIV Unit, University Hospital Germans Trias i Pujol, Barcelona, Spain, the study will be conducted at clinical sites in France, Spain, Italy, and the United Kingdom.

The EraMune 01 study, "International, multicenter, randomized, non-comparative controlled study of therapeutic intensification plus immunomodulation in HIV-infected patients with long-term viral suppression," is a further investigation of Cytheris' promising investigative immunotherapy, CYT107 (recombinant human interleukin-7, or IL-7), already the subject of seven other studies for different indications.

"The novelty of the approach in this study is three-fold," said Prof. Katlama. "First, the use of highly potent antiretroviral therapy combining drugs with different HIV enzyme targets or receptors and different penetrations in cells, to suppress the virus to truly undetectable levels; secondly, the addition of an immunomodulatory therapy that specifically targets viral reservoirs; and lastly, the rigorous selection of patients already having a low HIV reservoir as measured by peripheral blood HIV DNA content."

Eradication of HIV from an infected individual cannot be achieved by any of the current antiretroviral drug regimens in use today. To date, the failure to eradicate HIV has been due to viral persistence in reservoirs that are established early in the infection and are insufficiently affected by antiretroviral therapy, and thus are able to replenish systemic infection whenever treatment is interrupted. Highly active antiretroviral therapy can reduce plasma viral load below detectable limits in most patients. However, the current therapies target various steps in the virus life cycle, which results only in prevention of new infection with little impact on already infected cells or the integrated provirus.

"IL-7 in combination with conventional antiretroviral therapy has demonstrated in early clinical studies that it promotes restoration of T cell numbers and function and induces some HIV replication in the CD4+ T cell subset, including quiescent T cells, while also expanding the pool of uninfected CD4+ T cells," said Therese Croughs, MD, Chief Medical Officer of Cytheris. "The unique hypothesis tested in this study is that with a novel antiretroviral therapy combination complemented by entry and integrase inhibitors, the induction of viral replication from quiescent CD4+ T cells can be contained by the complementary HIV inhibitors while remaining sufficient to expose infected cells to immune elimination, eventually contributing to viral reservoir reduction and potential eradication."

In the last two decades, 27 antiretroviral drugs have been approved by the FDA and EMEA, including two new recently approved classes of drugs, the integrase inhibitor raltegravir (Isentress—Merck & Co.) and the CCR5 inhibitor, maraviroc (Selzentry—ViiV Healthcare). The goal of eradication of HIV from the host has resurfaced because of these additional new classes of drugs.

One of the most exciting areas in HIV treatment and research today involves the integrase inhibitors. Integrase is an HIV viral enzyme that is essential for viral replication. Inhibitors of integrase are completely independent in their activity compared to all other antiretroviral drug classes including reverse transcriptase, protease, maturation and entry inhibitors. Viruses resistant to all known drugs therefore, remain completely susceptible to integrase inhibitors. Additionally, integrase inhibitors are active in both CCR5-tropic and CXCR4-tropic HIV-1 viruses.

The overall strategy of the EraMune 01 trial is to treat selected patients with an optimal synergistic antiretroviral regimen plus one or more immunomodulating agents.

In summary, the EraMune Program proposes a proof of concept strategy that combines the association of novel safe and very potent ARVs with an optimized cART [combination antiretroviral therapy] regimen plus an immune experimental intervention that would activate the latently infected cells in order to purge the reservoir of HIV-infected patients while the antiviral combination would block the spread of the virus. The patients will be selected on the basis of a low peripheral blood reservoir. The proposed immune intervention has been shown to be safe in vivo. The concept will ultimately test whether
exhausting the HIV reservoir and ultimately obtaining virus eradication is feasible. If successful, this would open the door for more innovative approaches that would be capable of eradicating the virus in a broader spectrum of patients.

**About the Study—**[www.clinicaltrials.gov](http://www.clinicaltrials.gov)

Antiretroviral therapy (ART) has been one of the most successful fields of therapeutic research in the last twenty years. The extensive use of highly active antiretroviral therapy (HAART) since 1996 has led to a marked decrease in morbidity and mortality of HIV-1 infection, transforming a uniformly lethal disease into a chronic infection. The goal of therapy is a durable suppression of viral replication, the almost unique condition for immune reconstitution, control of disease progression, prevention of the emergence of drug resistance, and, ultimately, potentially normal life span. However, in the absence of any alternative treatment to durably control viral replication and the lack of current strategy to eradicate HIV from an infected person, antiretroviral therapy has to be administered life-long. Nevertheless, life-long use of antiretroviral therapy raises other crucial issues such as long-term tolerability and compliance, risk of emergence of resistance in case of incomplete viral suppression, sustainability of drugs supplies worldwide.

The first step in developing a new therapy and the focus of this study is to explore the strategy of ARV treatment intensification with the addition of an immunomodulating agent that can activate latently-infected cells. This will be undertaken in a pilot study in patients with fully controlled HIV replication as measured by viral RNA and cell-associated HIV DNA. The first proof of concept clinical study outlined here will include 28 patients, each randomized in an open label non-blinded manner to one of two study arms (14 per group):

A. Antiretroviral intensification (cART + raltegravir and maraviroc)
B. Antiretroviral intensification + immunomodulatory intervention (added after 8 weeks of antiretroviral intensification) with 2 cycles of 3 r-hIL-7 (CYT107) injections.

**Primary objective:**
- Important decrease in the HIV-1 viral reservoir

**Secondary objectives:**
- Eradicate HIV in the lymphoid reservoirs of HIV in the gut;
- To describe the immunologic effects of treatment intensification with and without immunomodulatory therapy;
- Develop a model for HIV DNA decay in patients receiving treatment intensification with and without immunomodulatory therapy;
- Determine the safety of treatment intensification with and without immunomodulatory therapy.

**About Interleukin-7 (CYT107)**

Recombinant human interleukin-7 (CYT107) is a critical immune-modulator for immune T-cell recovery and enhancement. As a growth factor and cytokine physiologically produced by marrow or thymic stromal cells and other epithelia, IL-7 has a critical and, at some steps, a non-redundant stimulating effect on T lymphocyte development, notably on thymopoiesis and, downstream from the thymus, on homeostatic expansion of peripheral T-cells.

A first-generation form of rhIL-7 was shown in pre-clinical and Phase I studies in oncology and HIV-infected patients to be well tolerated in repeated dose trials, with long-lasting increases in both CD4 and CD8 T cells. CYT107 is a second-generation rhIL-7 product made by Cytheris via a recombinant mammalian cell culture system.

Clinical trials conducted on more than 160 patients (90 with CYT107) in Europe, North America and Taiwan have demonstrated the potential of IL-7 to expand and protect CD4+ and CD8+ T-cells. Currently, Cytheris is conducting multiple international investigations of IL-7 in HIV, HCV, HBV, post-BMT and cancer. Additional studies include a NIAID/NIH-sponsored trial in idiopathic CD4 lymphocytopenia (ICL) and a cancer vaccine study in children with Ewing’s sarcoma family of tumors or similar genetic tumors sponsored by US National Cancer Institute.

**About Cytheris—**[www.cytheris.com](http://www.cytheris.com)

Cytheris SA is a privately held clinical-stage biopharmaceutical company focused on research and development of new therapies for immune modulation. These drugs aim at reconstituting and enhancing the immune system of patients suffering from cancer, chronic viral or bacterial infections such as HCV, HBV and HIV, or lympho-depleting treatments such as chemotherapy, radiotherapy, bone marrow transplantation (BMT) and hematopoietic cell transplantation (HCT). The company operates from its headquarters and laboratories in Issy-les-Moulineaux, a suburb of Paris, and its U.S. subsidiary in Rockville, Maryland. 10/22/10
**Intensification of Antiretroviral Therapy Does Not Eliminate HIV in Gut or Central Nervous System**

**SUMMARY:** Intensifying antiretroviral therapy (ART) by adding raltegravir (Isentress) and other agents to an existing suppressive regimen did not lead to HIV viral load decreases in the blood or gut, researchers recently reported. In a related study, adding drugs—including those with good blood-brain barrier penetration—did not reduce virus levels or immune activation in the cerebrospinal fluid surrounding the brain and spinal cord. Taken together, these findings add to the evidence that residual HIV is not attributable to low-level ongoing replication.

**By Liz Highleyman**

Despite use of effective antiretroviral drugs that suppress viral load to an "undetectable" level using standard tests, ultra-sensitive assays can almost always detect very low levels of residual virus. To date, use of ART alone has not been able to eradicate HIV.

Researchers working on a cure for AIDS have debated whether this residual virus is attributable to continued low-level replication—in which case more potent antiretroviral therapy might succeed in eliminating it—or due to virus "leaking" out of reservoirs such as resting CD4 T-cells or anatomic sites such as the brain where antiretroviral drugs may not reach.

**HIV in the Gut**

As reported in the October 23, 2010 issue of *AIDS*, Steven Yukl from the San Francisco VA Medical Center and colleagues assessed whether adding raltegravir to an already suppressive ART regimen could reduce HIV levels in the gut. This work was also presented at the XVIII International AIDS Conference (AIDS 2010) this summer in Vienna and at a preceding International AIDS Society workshop on HIV reservoirs.

This open-label study included 7 HIV positive adults on a stable ART regimen with plasma HIV RNA < 40 copies/mL. Participants received 12 weeks of ART intensification by adding raltegravir—an integrase inhibitor that prevents HIV from inserting its genetic material into host cell chromosomes—either alone or in combination with the NNRTI efavirenz (Sustiva) or the protease inhibitor darunavir (Prezista).

The researchers collected cells from the gut via upper and lower endoscopy at baseline and after 12 weeks, taking biopsy samples from the duodenum (first section of the small intestine connected to the stomach), ileum (final section of the small intestine), colon (large intestine), and rectum.

Study outcomes included blood plasma HIV RNA, HIV DNA and RNA from peripheral blood mononuclear cells (PBMCs), viral genetic material at the 4 gut sites, levels of T-cell subsets, and various immune activation biomarkers.

**Results**

- ART intensification produced no consistent decrease in HIV RNA in the plasma, PBMCs, duodenum, colon, or rectum.
- 5 of the 7 patients, however, showed a decrease in unspliced HIV RNA in CD4 T-cells in the ileum.
- There was a non-significant trend towards decreased T-cell activation at all sites.
- The largest decrease in activation was observed for CD8 T-cells in the ileum and PBMCs.
- There was also a trend towards increased CD4 T-cells in the ileum.

"Most HIV RNA and DNA in the blood and gut is not the result of ongoing replication that can be impacted by short-term intensification with raltegravir," the investigators concluded.

However, they added, "the ileum may support ongoing productive infection in some patients on ART, even if the contribution to plasma RNA is not discernible."

**Virus in the CNS**

In the second study, published in the September 16, 2010 advance online edition of the *Journal of Acquired Immune Deficiency Syndromes*, Aylin Yilmaz from the University of Gothenburg in Sweden and an international team of colleagues looked at the effect of ART intensification on HIV levels in the central nervous system (CNS).

Antiretroviral drugs differ in their ability to cross the protective blood-brain barrier to reach HIV in the CNS. Overall, ART significantly reduces HIV RNA in the cerebrospinal fluid (CSF) surrounding the brain and spinal cord, and residual virus is detected less frequently in CSF than in blood, the study authors noted as background. But persistent CNS immune activation is commonly observed even after several years of treatment.

In this study, the researchers sought to determine whether low-level CSF viral load and residual immune activation within the CNS result from ongoing local viral replication or from some other source.
The analysis included 10 patients who at the start of the study had been on suppressive ART with plasma HIV RNA < 50 copies/mL for more than 18 months (median 6.5 years). Most were men, the mean age was 52 years, and the median CD4 cell count was relatively high at 465 cells/mm³. At the start of the study, ultra-sensitive tests showed a median plasma viral load of 5 copies/mL and a median CSF viral load of 2 copies/mL.

Participants intensified therapy by adding maraviroc (Selzentry) or lopinavir/ritonavir (Kaletra)—2 drugs with good CNS penetration—for 4 weeks, followed by enfuvirtide (T-20; Fuzeon), which has poor CNS penetration, for an additional 4 weeks.

The researchers performed lumbar punctures, or spinal taps, 4 weeks before ART intensification, at the start of intensification, at the switch-over after the first 4 weeks, at the end of the second 4 weeks, and 4 weeks after the intensification period.

**Results**

- No significant changes were seen in HIV RNA levels in plasma or CSF, before, during, or after ART intensification.
- Similarly, other HIV and immune activation biomarkers in plasma and CSF did not change during the study, including neopterin, beta-2-microglobulin, immunoglobulin G index, albumin ratio, and CD4 T-cell count.

Based on these findings, the researchers concluded, "Treatment intensification with a potent CNS-penetrating antiretroviral drug does not reduce residual CSF HIV RNA levels or intrathecal [around the spinal cord] immune activation."

These findings, they said, do not support the hypothesis that residual CSF viral load and immune activation in the CNS are mainly attributable to ongoing viral replication.

**References**


**Cholera Kills 138 People, More Than 1,500 Other Cases Reported, Haitian Health Ministry Officials Say**

"Haitian Health Ministry officials have informed the World Health Organization that 138 deaths are a part of a fast-moving cholera outbreak north of Port-au-Prince, a U.N. official said," CNN reports. In addition to the deaths, 1,526 cases of cholera have been reported in the Lower Artibonite region, said Imogen Wall, the U.N. humanitarian spokesperson in Haiti. "This is a situation that's developed very quickly. It’s only been 48 hours, and we’ve already got 138 deaths confirmed," Wall said (10/22).

According to Wall, the WHO and U.N. have not yet confirmed cholera as the cause and are awaiting results from laboratory tests on samples taken from the dead and the sick, Reuters reports (Delva, 10/21). "No cholera outbreaks had been reported in Haiti for decades before the earthquake, according to the U.S. Centers for Disease Control and Prevention. Haitian officials, including President Rene Preval, have been pointing to the lack of severe disease outbreaks as a hard-to-see success of the quake response," the Associated Press writes (Kushner, 10/22).

Michel Thieren, a physician with the Pan American Health Organization, "described the outbreak as 'severe,' and noted that officials were still trying to track how far it had spread," according to CNN. "This is an unprecedented episode of cholera, and the government needs a lot of support, and they need to be vigilant in how they respond," Thieren said (10/22).

On Wednesday, U.N. aid workers said they were investigating disease outbreaks in the town of St. Marc and the Arbonite, the Canadian Press reports. "The Arbonite is Haiti’s most important farming region. The area was not severely damaged in the Jan. 12 earthquake but received thousands of refugees from the wrecked capital to the south, many of whom stayed" (Katz, 10/21).

Agence France-Presse notes: "Aid agencies have voiced fears for months that any outbreak of disease could spread rapidly due to the unsanitary conditions in the camps where people have little access to clean water. International agencies have swung into action, mobilizing medical personnel to try to contain the spread of the disease and treat the sick. 'We are evaluating the situation on the ground with the international partners and the Haitian health authorities,' said Fanny Devoucoux from the French aid organization Acted" (Renois, 10/21).
"The outbreak could be another failure on a growing list that has many here, and elsewhere in the world, wondering if the United Nations and its secretary general, Ban Ki-moon, are fulfilling its humanitarian role," GlobalPost writes in an article examining criticisms of the U.N.'s approach to Haiti after the earthquake. "Despite the scale of tragedy, some analysts have likened Ban's response to that of President George W. Bush's response to Hurricane Katrina: slow, underwhelming and off-message."

Farhan Haq, Ban's acting deputy spokesperson, pointed out, "As for the compound, the main U.N. compound in Haiti was itself destroyed in the earthquake. The United Nations is hardly disconnected from the reality faced by Haitians, having itself lost 101 staff" (O'Connor, 10/21).

Researchers Find Evidence That A. Gambiae Mosquito Is Evolving Into Two Strains, Could Present Challenges For Malaria Control Efforts

The Anopheles gambiae mosquito, "one of the major carriers of the malaria parasite in Sub-Saharan Africa, is evolving in two directions," according to two studies published Thursday in the journal Science, Scientific American's "Observations" blog reports. "Some 247 million people were infected with malaria as of 2008, according to the World Health Organization, and it is implicated in about one million deaths each year," the blog adds (Harmon, 10/21).

"The revelation could present real difficulties in controlling malaria because eradication strategies directed against one mosquito species may not be effective against another, according to the scientists who discovered the genetic differences between the two strains," the Independent reports (Connor, 10/22).

As one of the "top carriers of malaria parasites," researchers have focused much attention on the A. gambiae mosquito, LiveScience/MSNBC.com writes. "In recent years, researchers observed that A. gambiae seemed to be differentiating into two species," according to the article (10/21).

To better understand the differences between the two lineages, a group of researchers from the Imperial College London, the University of Notre Dame, the J. C. Venter Institute, Washington University and the Broad Institute "carried out the most detailed analysis so far of the genomes of the M and S strains of Anopheles gambiae mosquito, over two studies," according to a Imperial College London press release.

"The first study, which sequenced the genomes of both strains [from colonies collected from Mali], revealed that M and S are genetically very different and that these genetic differences are scattered around the entire genome. ... The work suggested that many of the genetic regions that differ between the M and S genomes are likely to affect mosquito development, feeding behaviour, and reproduction," according to the press release (10/21).

In the other study "researchers compared key genetic differences between these two A. gambiae types (in addition to the Bamako strain, which falls into the S subtype) [from Mali and Cameroon]," the "Observations" blog adds. "Their study found that, based on genetic sites that seemed to have changed the most, the mosquitoes might be diverging in part due to habitat differences" (10/21).

"From our new studies, we can see that mosquitoes are evolving more quickly than we thought and that unfortunately, strategies that might work against one strain of mosquito might not be effective against another," Mara Lawniczak of Imperial College London, lead author of the studies, said, the Press Association/Guardian reports. "It's important to identify and monitor these hidden genetic changes in mosquitoes if we are to succeed in bringing malaria under control by targeting mosquitoes" (10/21).

LiveScience/MSNBC.com elaborates on the differences between the environments where M and S strains appear to thrive, as described by Notre Dame Biologist Nora Besansky, a co-author on the studies: "S seems to prefer breeding in temporary pools and puddles, Besansky said, while M is more adapted to irrigated habitats like rice fields. ... The difference in environments represents a trade-off. Puddles are light on predators; so S mosquito larvae can expend energy on quick growth without great risk of getting eaten. Exploiting human irrigation, M mosquitoes can grow and breed even in dry areas, but they may have to adapt to avoid predators in these more-permanent environments. For humans, this ecological efficiency is bad news, Besansky said."

"Because M is able to exploit areas that tend to be drier and seasons that are drier, this has resulted in malaria spreading in both space and time," Besansky explained (10/21).

"Future research will further investigate these emerging species, exploring how they compete with one another in various habitats and the molecular basis of their evolution. The results will be used to refine existing malaria interventions and inform the development of new disease prevention strategies,"
according to an NIH/National Institute of Allergy and Infectious Diseases (NIAID) press release. The studies were funded, in part, by the NIAID (10/21).

Iowa State, Ames Lab chemists discover proton mechanism used by flu virus to infect cells

AMES, Iowa – The flu virus uses a shuttle mechanism to relay protons through a channel in a process necessary for the virus to infect a host cell, according to a research project led by Mei Hong of Iowa State University and the Ames Laboratory.

The findings are published in the Oct. 22 issue of the journal Science.

Hong, an Iowa State professor of chemistry and an associate of the U.S. Department of Energy's Ames Laboratory, said her research team used solid-state nuclear magnetic resonance (NMR) spectroscopy to determine the structure and workings of the proton channel that connects the flu virus to a healthy cell. She said a full understanding of that mechanism could help medical researchers design drugs that stop protons from moving through the channel.

That proton channel is an important part of the life cycle of a flu virus. The virus begins an infection by attaching itself to a healthy cell. The healthy cell surrounds the virus and takes it inside through a process called endocytosis. Once inside the cell, the virus uses a protein called M2 to open a channel. Protons from the healthy cell flow through the channel into the virus and raise its acidity. That triggers the release of the virus' genetic material into the healthy cell. The virus then hijacks the healthy cell's resources to replicate itself.

Hong and her research team – Fanghao Hu, an Iowa State doctoral student in chemistry; and Wenbin Luo, a former Iowa State doctoral student who is now a spectroscopist research associate at Penn State University – focused their attention on the structure and dynamics of the proton-selective amino acid residue, a histidine in the transmembrane part of the protein, to determine how the channel conducts protons. Their work was supported by grants from the National Science Foundation and the National Institutes of Health.

Two models had been proposed for the proton-conducting mechanism:

• A "shutter" channel that expands at the charged histidine because of electrostatic repulsion, thus allowing a continuous hydrogen-bonded water chain that takes protons into the virus.
• Or a "shuttle" model featuring histidine rings that rearrange their structure in some way to capture protons and relay them inside.

Hong’s research team found that the histidine rings reorient by 45 degrees more than 50,000 times per second in the open state, but are immobile in the closed state. The energy barrier for the open-state ring motion agrees well with the energy barrier for proton conduction, which suggests that the M2 channel dynamically shuttles the protons into the virus. The chemists also found that the histidine residue forms multiple hydrogen bonds with water, which helps it to dissociate the extra proton.

"The histidine acts like a shuttle," Hong said. "It picks up a proton from the exterior and flips to let it get off to the interior."

The project not only provided atomic details of the proton-conducting apparatus of the flu virus, but also demonstrated the abilities of solid-state NMR.

"The structural information obtained here is largely invisible to conventional high-resolution techniques," the researchers wrote in their Science paper, "and demonstrates the ability of solid-state NMR to elucidate functionally important membrane protein dynamics and chemistry."

How H1N1 differs from other viruses as a respiratory illness

Findings of study from Rhode Island Hospital to be presented at IDSA annual meeting

PROVIDENCE, RI—The 2009/2010 Influenza A (H1N1) is one of several viruses responsible for respiratory-related infections. A new study from Rhode Island Hospital examined patients with viruses and found distinguishing characteristics of the H1N1 virus in how it affects respiratory illness. Their findings will be presented at the annual meeting of the Infectious Diseases Society of America to be held in Vancouver, Canada on Friday, Oct. 22.

Phil Chan, MD, an infectious diseases fellow at Rhode Island Hospital, studied the signs, symptoms, and laboratory findings of 668 adult and pediatric patients who were treated at Rhode Island Hospital or its partner, The Miriam Hospital, between October and December 2009 with a confirmed viral infection.
Chan says, "Compared to patients with other viruses, individuals with novel Influenza A, or H1N1, were more likely to present with subjective fever, cough, sore throat, nausea/vomiting. The mean white blood count of patients with H1N1 is lower than with other viruses as well."

Leonard Mermel, DO, medical director of epidemiology and infection control at Rhode Island Hospital and professor of medicine at The Warren Alpert Medical School of Brown University, is a co-author. Mermel adds, "Perhaps more striking is that patients with the novel Influenza A virus may have higher mortality rates compared to other respiratory viruses in the patients studied. As a result of this study, and based on available data in the literature, we recommend that high-risk patients infected with novel Influenza A receive expedient antiviral therapy." Mermel is also a physician with University Medicine.

In his presentation, Chan will provide more details on the findings of this study.

**Swine flu variant linked to fatal cases might have disabled the clearing mechanism of lungs, study suggests**

22 Oct 2010

A variant of last year's pandemic influenza linked to fatal cases carried a mutation that enabled it to infect a different subset of cells lining the airway, according to new research. The study, due to be published next week in the *Journal of Virology*, suggests that the mutant virus could have impaired the lungs' ability to clear out germs. The researchers behind the study, from Imperial College London, the Medical Research Council National Institute for Medical Research and the University of Marburg said the findings highlight the potential for deadlier strains of flu to emerge and spread.

The 2009 pandemic of H1N1 influenza caused thousands of deaths worldwide, but the majority of cases were relatively mild. A *variant of the virus carried a mutation termed D222G in a protein on the surface of the virus, and people infected with this variant were more likely to have severe and fatal illness*. According to a World Health Organisation report, the D222G mutation was found in less than two in every hundred cases of 2009 pandemic flu, but was responsible for around seven in every hundred deaths.

Viruses infect cells by attaching to receptor molecules on the cell surface. Different receptors are present on different cell types, and a virus can only infect cells that have the right receptors for the protein on its own surface.

The new research shows that *flu virus with the D222G mutation can bind to a broader range of receptors in the airway, including receptors that are present on cells called ciliated cells*. These cells, found in the lining of the airway, have hair-like projections called cilia. The cilia sway back and forth to move mucus with trapped particles upward toward the mouth, and this is normally swallowed or coughed up. When *ciliated cells become infected, the cilia stop moving and this vital clearance function is impaired*. Inhaled viruses and bacteria can then reach the lung more easily, where they can potentially cause pneumonia.

The mutant virus has an increased capacity to infect ciliated cells, as shown by the collaborating group at the University of Marburg. Infection of the ciliated cells would sabotage the lungs' clearing mechanism and could be one factor that made the D222G mutation more virulent, the researchers suggest.

“This simple mutation, which swapped one building block of a virus protein for another, apparently resulted in a more virulent version of the H1N1 virus,” said Professor Ten Feizi from the Department of Medicine at Imperial College London, who led the study. “We think this is at least partly due to the virus being able to bind to different receptors, which allowed it to infect ciliated cells and stop them from clearing out germs.

“If the mutant virus were to acquire the ability to spread more widely, the consequences could be very serious. The study goes to show how important it is that the WHO Global Influenza Surveillance Network continues to monitor closely the emergence of new variants of the flu virus. Even though the 2009 pandemic was relatively mild, it's vital that we handle outbreaks cautiously and stay vigilant. The virus is constantly evolving, and it's possible that a new form as dangerous as the 1918 pandemic could emerge.”

Professor Feizi and her team study the receptor specificity of different flu viruses by attaching onto a glass surface a range of different carbohydrates, resembling the receptors present on the surface of airway lining cells. The virus is then incubated on top of the glass surface, and using a fluorescent dye, the researchers can see the receptors on the plate to which the virus binds.

The study builds on *earlier work* by Professor Feizi and her colleagues which showed that compared with seasonal influenza, the 2009 pandemic virus could bind to a broader range of receptor types. The previous study showed that pandemic flu had some affinity for so-called alpha2-3 receptors, as well as the
alpha2-6 receptors favoured by seasonal flu. Now they have shown that this affinity for alpha2-3 receptors is substantially enhanced in cases of pandemic flu with the D222G mutation. Whereas alpha2-6 receptors are found in the nose, throat and upper airway, alpha2-3 receptors are prevalent in the lung but also on ciliated cells throughout the respiratory system.

Mount Sinai researchers discover origin of immune cells in the brain
Mount Sinai researchers have discovered that microglia, the immune cells that reside in the brain, have a unique origin and are formed shortly after conception. It was previously thought that microglia originated at the same time as macrophages, which are other immune cells that are thought to develop at birth. This groundbreaking discovery has the potential to lead to future treatments of degenerative brain diseases such as Alzheimer's and autoimmune diseases such as multiple sclerosis. The study is published online October 21 in Science Express.

Microglia are thought to play an important role in the development of many brain diseases, and that defective microglia could lead to the release of inflammatory molecules, which could participate in the development of degenerative brain diseases.

"This really is a startling discovery," said Miriam Merad, MD, PhD, Associate Professor of Gene and Cell Medicine at Mount Sinai School of Medicine and Principal Investigator of the study. "We've shown that the precursor cells develop into microglia only during a short period after conception. Now that we know that microglia originate in early embryos, theoretically we should be able to generate microglia from embryonic stem cells to treat brain diseases caused by defective microglia. This is a very good example of why scientists need to be able to conduct research with embryonic stem cells."

For the first part of the study, researchers transplanted blood cell precursors, which are precursors for all macrophages, from one newborn mouse to another. The transplanted cells could not be differentiated in the recipient animal. These results suggest that microglia originated prior to birth during embryonic life.

Next, researchers used a mouse model that expresses fluorescent biosensors in blood precursors to determine when, during embryonic age, precursors develop into microglia. Once activated the fluorescence does not go away and all cells that develop from the fluorescent precursors should remain fluorescent. The researchers activated the fluorescence as early as seven days after conception. When they examined adult mice they found fluorescent microglia but no fluorescent macrophages. These results established that microglia are unique in that they originate from precursors that arise around seven days after conception.

"Moving forward we need to further study the normal development of precursor blood cells into microglia, which should help identify the role of microglia in various brain diseases and ultimately lead to advances in treatments," said Dr. Merad.

Natural Killer Cells May Limit Inflammation in the Central Nervous System
ScienceDaily (Oct. 22, 2010) — Scientists at Barrow Neurological Institute have recently made discoveries about a type of cell that may limit inflammation in the central nervous system (CNS)—a finding that could have important implications in the treatment of brain disorders such as multiple sclerosis.

The research, led by Barrow’s Fu-Dong Shi, MD, PhD, was published in the August 2010 issue of The Journal of Experimental Medicine, and simultaneously highlighted in Nature.

Dr. Shi directs the Neuroimmunology Laboratory and Flow Cytometry Core Facility at Barrow. One of his research interests is natural killer (NK) cells, a type of immune cell that destroys tissue that has been infected by pathogens and malignant cells. While recent research has shed more light on the role of NK cells in other parts of the body, Dr. Shi’s research is unveiling important discoveries about how NK cells work in the CNS.

In multiple sclerosis, the body’s immune system attacks myelin, a protective sheath surrounding nerve cells in the brain and spinal cord. By studying a pre-clinical model of multiple sclerosis, the Barrow research revealed that enriching an affected area with NK cells improved disease symptoms, while blocking NK cells to the CNS made symptoms worse. The research indicates that NK cells—especially those that originate in the CNS, as opposed to NK cells from peripheral organs—play a critical role in controlling the magnitude of CNS inflammation and immune response.

"These studies provide novel insight into the biology of NK cells and might lead to the design of NK cell-based approaches for intervention in inflammatory and autoimmune disorders of the central nervous
"system," says Dr. Shi. "Our findings have important implications for understanding the efficacy of some drugs currently used in CNS diseases such as multiple sclerosis."

**Journal Reference:**

By Jef Akst

**Brain cell origin solved**

**Brain macrophages are derived from cells in the embryonic yolk sac, finally solving an ongoing controversy in neuroscience**

[Published 21st October 2010 07:00 PM GMT]

New findings lay to rest a debate over the origin and cell lineage of macrophages found in mouse brains—they come from progenitor cells in the embryonic yolk sac and are self-renewing, and are not derived from bone marrow precursors like other macrophages in the body. The results, published online today (21 October) in *Science Express*, may also hold implications for the treatment of neurodegenerative diseases.

"It has been quite controversial where [microglia] come from in embryonic life," said neurologist Richard Ransohoff of the Cleveland Clinic, who was not involved in the research. This study "showed unequivocally that microglia come from these yolk sac progenitors."

Microglia are macrophages that reside in the central nervous system. They are important for maintaining healthy brain function and have been associated with many neurodegenerative and brain inflammatory diseases, but where they come from—both initially and throughout life—has been a bit of mystery.

Some mice studies suggested that they could be replaced by bone marrow progenitor cells, but a couple of papers published in *Nature Neuroscience* in 2007 suggested that these experiments, which involved irradiating the animals, introduced artifacts and were "completely un-physiological," Ransohoff explained. Whether or not the bone marrow could contribute to the microglia in the brain under normal conditions has remained unclear, as has where the microglia cells came from initially.

To answer these questions, immunologist Miriam Merad of the Mount Sinai School of Medicine in New York and her colleagues created mice with green fluorescent protein (GFP) attached to the fractalkine receptor (CX3CR1), which is found on early myeloid progenitors and microglia. Monitoring the mice, they saw evidence of microglia when the embryos were around 10.5 days old, and the phenotype of the cells suggested they were derived from the yolk sac.

To confirm this, the researchers labeled the yolk sac cells with yellow fluorescent protein (YFP) at various times throughout development, and watched where they went. They found that some myeloid progenitor cells in the yolk sac indeed became microglia, and the cells that give rise to microglia are produced in a very limited time window, around days 7 to 8 of embryonic development. Furthermore, only a few percent of circulating and non-brain tissue macrophages carried the YFP label, suggesting they were derived from another source.

"The paper is highly influential," developmental neuroscientist Payam Rezaie of The Open University in the UK, who did not participate in the research, told *The Scientist* in an email.

The authors went on to show that bone marrow progenitor cells do not contribute to the microglia in the healthy adult brains, in contrast to when the mice are irradiated. This supports the notion that resident microglia (i.e. the embryo-derived cell population) are maintained independently through self-renewal.

"In a normal healthy animal, the majority of cells that appear to populate the adult brain are derived from the yolk sac in the embryo...and they persist for a long time," said neuroimmunologist Hugh Perry of the University of Southampton, who was not involved in the study.
What this means for the function of these cells is unclear, however, he added. After irradiation, for example, bone-marrow derived cells that look like microglia do end up in the brain, meaning that "macrophage cells have the capacity to enter the brain and adopt the morphology of microglia" under some conditions, Perry said.

The results could have therapeutic implications for neurological diseases, said Ransohoff. "Your strategy for dealing with the bad consequences of microglial or macrophage activation in neurological disease are going to depend on where you think they came from," he said. If the cells are coming from the bone marrow, a logical solution would be to block them from getting to the brain in the first place, he explained. On the other hand, if the resident microglia are the problem, they are already in the brain, so "you have to come up with compounds that directly address microglial activation," he said. "Those are two totally different therapeutic strategies."

Additionally, this research emphasizes the importance of embryonic work, study author Merad told The Scientist. "Our work reveals that there are processes that only occur during early embryonic life," she said. "That shows that we need to work on embryos if we want to understand all the molecular program to make these cells.[and] the biology of these brain diseases."


By Quentin J. Sattentau and Andrew J. McMichael

**Templates for a vaccine?**

**New tools for HIV-1 antibody-based vaccine design**

The human immunodeficiency virus type-1 (HIV-1) continues its global spread, with an estimated 33 million people infected. The most cost-effective mechanism of infectious disease control is vaccination, but to date vaccine trials have had only modest success at reducing HIV-1 spread.1

However, antibodies that block HIV-1 infection, termed neutralizing antibodies (NAbs), are known to be effective in preventing HIV-1 infection. Unfortunately, current vaccines have been unable to induce the host to produce this type of antibody. The immune system mounts an immune response to HIV-1 that includes the production of antibodies that bind the viral envelope glycoprotein (Env), the target of neutralizing antibodies. However, naturally produced antibodies are insufficient to curtail infection in most people. One reason is that the Env gene has a strong propensity to randomly mutate its amino acid sequence, rendering antibodies produced against an early version of the glycoprotein ineffective at binding a subsequent version. Therefore, most NAbs produced by the host will only bind to a small subset of total HIV-1 strains that are produced over the course of an infection.

One way around this problem is to direct the immune system to create antibodies that target regions of Env that the virus cannot afford to mutate, for instance, the surface subunit of Env, termed gp120,2 which allows the virus to dock onto the host cell’s CD4 molecule, a critical first step in entry. Other conserved regions of Env are also involved in viral entry, such as the gp41 Env subunit that induces fusion of the viral membrane with the cell membrane. Several neutralizing monoclonal antibodies (NMABs—NAbs of a single specificity) of human origin were discovered over a decade ago that associate with these conserved regions of Env. Much interest has been generated by the idea that antibodies such as these might be used as tools for vaccine design.
Template-based vaccine design

Relatively recently, the concept of using NMAs as templates for antibody-based vaccine design has emerged in the field. The idea is to engineer a piece of protein that mimics the segment of the antigen to which the antibody binds (called the epitope), and therefore looks like an isolated segment of the original antigen.4 If researchers could define the structural characteristics of the portion of Env that binds the NMAb, then they could generate a protein with an epitope that binds the NMAb using current protein engineering techniques. This protein epitope could then be used as a vaccine that elicited specific and evolution-resistant viral antibodies.

Until this past year, only four NMAs were available. Although the antigen binding regions of all these NMAs are structurally defined and have been excellent prototypes for studying neutralization, each one had specific structural and biochemical problems that made their use as templates for vaccine design difficult.4 Also, it is unlikely that an antibody response trained against the shape of one binding region would protect against all possible virus variants—a caveat that potentially limits the breadth of such a vaccine.

**New templates**

The breakthrough that has come in the past year is the isolation of new human NMAs that neutralize a broad spectrum of HIV-1 strains, and therefore must bind to conserved regions of Env. The first such novel specificities were reported by Dennis Burton and colleagues at the Scripps Research Institute in La Jolla, in the form of two related NMAs (PG9 and PG16) that neutralized approximately 80–90 percent of representative HIV-1 strains with potencies approximately 10-fold greater than the previous NMAs.2 They were cloned from B cells of an HIV-1–infected individual with an unusually broad serum neutralization activity, and were found to bind complex epitopes only present on the functional, membrane-anchored Env structure rather than on soluble engineered mimics of Env. A second NMAb (HJ16), which neutralizes approximately 35 percent of HIV-1 strains, can be robustly expressed on a soluble engineered form of gp120 under various conditions, suggesting that it may be particularly amenable for use as a template in vaccine design. Finally, two very recent studies report on the isolation of three NMAs (VRC01, 02, and 03) that neutralize up to 90 percent of circulating strains of virus at low concentration. Such potent and broad neutralizing activity in HIV-1–infected individuals gives hope that vaccine antigens based on one or a few epitopes may be sufficient to protect the majority of the population from infection.

The challenge now is to translate this information into a functional vaccine: this will require cutting-edge antigen design technology using structural biology associated with molecular modelling, genetic engineering and high-quality biochemical purification and characterization of the resulting antigens. This process will need to be associated with a better understanding of how to optimize the antibody response to HIV-1 Env. For example, we do not understand the relationship between the surfaces exposed on an antigen (“antigenicity”) and the ability of those surfaces to elicit the desired immune response (“immunogenicity”). Fortunately, the intense international research focus on all elements of this problem are yielding progress, and the next 5 years will reveal whether template-based design will fulfill its potential in the context of HIV-1 vaccine development.

References:


By Jef Akst

Giant marine virus found

Researchers discover yet another virus with a large, complex genome, suggesting they may be fairly common

[Published 25th October 2010 08:00 PM GMT]
With a genome of more than 700 kilobases, a newly discovered virus marks the first giant virus known to infect a marine organism, and the second largest virus ever recorded.

The discovery, published this week in *Proceedings of the National Academy of Sciences (PNAS)*, adds to the growing list of giant DNA viruses and suggests that these viruses, which appear to obtain much of their large genomes from their hosts and other microorganisms, may be more commonplace than scientists once believed.

"It’s really interesting, and a completely different way of seeing viruses," said microbiologist Didier Raoult of the University of the Mediterranean in Marseille, France, who was not involved in the research. "It’s a completely new field that is emerging."

These viruses "are probably playing a big role in the genetic diversity of organisms in the ocean as well," said microbiologist James Van Etten of the University of Nebraska, who also did not participate in the study. Not only can viruses take up genetic material from their hosts and other organisms, but they can donate genes, as well, he said.

"If you’re teaching a beginning virology course now, it’d be pretty hard to ignore... that there are these very large DNA viruses in nature," said Van Etten, who edited the *PNAS* paper.

Over the past decade or so, scientists have slowly begun identifying viruses that defied the conventional idea that they were tiny infectious agents with highly streamlined genomes. In 2004, researchers discovered and sequenced the 1.2 million-base pair genome of the largest known virus to date, the mimivirus (although still dwarfed by sequenced multicellular organisms, whose genomes usually exceed 100 million base pairs). This virus, and most of the other recently discovered giant viruses, has been found in amoebae, which are sometimes referred to as "melting pots" because of all the microorganisms they ingest. Inside the amoebae, these viruses and bacteria may exchange their DNA and grow their genomes.

The new giant virus, dubbed CroV, is the first to be isolated from a marine organism—a microzooplankton called *Cafeteria roenbergensis*. They are major consumers of heterotrophic bacteria and phytoplankton, and thus critical to maintaining the delicate balance of marine food webs.

Once thought not to exist in marine environments, scientists now realize that there are some 50 million viruses in every milliliter of seawater. Every day, marine viruses kill about 20 percent of the ocean’s microorganisms, which produce about half the oxygen on the planet.

"These [viruses] are major players in the global ecosystem," said study author and marine virologist Curtis Suttle of the University of British Columbia.

Like amoebae, *C. roenbergensis* harbor many microorganisms simultaneously, making them "a good place to exchange genes," Raoult said. "When you live in a phagocytic protist, such as this one, you meet a number of microorganisms, and then you can exchange genes and get a bigger genome."

Indeed, of the 500 protein-coding genes Suttle and his colleagues found when they sequenced the virus’s genome, about half were similar to those in eukaryotes, bacteria, archaea, and other giant viruses. Those with known function included genes that code for translation factors, DNA repair enzymes, ubiquitin pathway components, and tRNAs.

"We’re finding suites of genes that you would really never expect to find in viral life, but would expect to find in cellular organisms," Suttle said.

"It is exciting to verify that [these large viruses] are out there," Van Etten said. There are likely many more, he added; "it’s just a matter of people looking."

**New model shows future impact of circumcision on Africa’s HIV epidemic probably underestimated**

Keith Alcorn
Published: 25 October 2010

Projections of the impact of circumcision on the HIV epidemic in sub-Saharan Africa based on clinical trials may underestimate the number of infections that can be averted by around 40%, according to an international group of epidemiological modellers.
The findings, published in advance online by the journal *Sexually Transmitted Infections*, come from new epidemiological modelling work that incorporates findings from a pooled analysis of three recent randomised trials that evaluated the impact of circumcision on HIV transmission from men to women.

The epidemiological modellers, from Imperial College, London, Weill Cornell Medical College, New York, and Fred Hutchinson Cancer Research Center, Seattle, took two existing models of the impact of circumcision on HIV incidence and applied data from a pooled analysis of two recent studies.

The models projected HIV incidence in Zimbabwe and Kisumu, Kenya, using data from a number of locally relevant studies to inform the assumptions about sexual behaviour.

However the original models lacked information about the rate of HIV transmission from circumcised men to women, and about the rate of HIV transmission during the period of wound healing after men were circumcised.

Neither model took into account the interaction between sexually transmitted infections (some of which increase the risk of HIV transmission) and circumcision (which may reduce the risk of men acquiring sexually transmitted infections).

In order to update the models, the epidemiologists took data from a pooled analysis of two studies which had each evaluated the rate of male-to-female transmission in circumcised men.

This pooled analysis found that from two years after the operation (when the effect begins to become apparent in trials and cohort studies) the rate of HIV transmission from circumcised men to women was reduced by 46%.

Assuming that only 50% of men remained uncircumcised after ten years and no men resume sex during the wound healing period, HIV incidence would be reduced by 20.5% in Zimbabwe, where no men had been circumcised before the intervention. In Kisumu, Kenya, where 25% of men were already circumcised, ensuring that half of all men are circumcised would lead to a 7.4% reduction in HIV incidence after ten years.

One concern about circumcision programmes is the potential for men to acquire or transmit HIV during the 4-6 week wound healing period after the operation. The modelling found that even if all men remained sexually active throughout the wound healing period – the most pessimistic assumption possible – HIV incidence would still fall by 19% in Zimbabwe and 6.2% in Kisumu after a decade.

Adding in the information about the rate of male-to-female transmission resulted in a greater projected reduction in HIV incidence. Over 20 years, HIV incidence would fall by 28% in Zimbabwe and 16.8% in Kisumu, and specifically among women, it would fall by 23.7% in Zimbabwe and 13.9% in Kisumu after 20 years.

The reduction in incidence could be as great as 43% after 20 years in Zimbabwe, and a reduction of at least 23% could be expected, the researchers calculated.

Fewer circumcisions would be required to avert each infection – 28% fewer in Zimbabwe and 41% fewer in Kisumu – implying that circumcision could be more cost-effective than previously calculated. The new figures show that assuming no change in sexual behaviour as a result of circumcision, previous projections underestimated the effect of circumcision on HIV incidence by at least 40% in Zimbabwe and by 79% in Kisumu.

The researchers say that “projections for the impact of circumcision interventions on population-level HIV may need to be dramatically revised: the impact of male circumcision implementation could be realised much sooner and with greater cost-efficiency than had previously been thought.”

Reference
Hallett TB, et al. *Will circumcision provide even more protection from HIV to women and men? New estimates of the population impact of circumcision interventions*. *Sex Transm Infect*, advance online publication, October 21 2010. ([Link to full text article](#))

**Swiss drug policy should serve as model: experts**

By Stephanie Nebehay

GENEVA | Mon Oct 25, 2010 1:02pm EDT

GENEVA (Reuters)—Switzerland’s innovative policy of providing drug addicts with free methadone and clean needles has greatly reduced deaths while cutting crime rates and should serve as a global model, health experts said on Monday.

Countries whose drug policy remains focused on punishing offenders, including Russia and much of Eastern Europe and Central Asia, should learn from a Swiss strategy based on “harm reduction” that protects both users and communities, they said.

Even Iran and China—while far from espousing Switzerland’s system of direct democracy—have copied its methadone substitution programs, they added.
The Alpine nation's experiment succeeded because Swiss political leaders adopted a pragmatic attitude toward an "uncontrollable" open drugs scene, according to a report "From the Mountaintops: What the World Can Learn from Drug Policy Change in Switzerland," by the Open Society Foundations. Soaring HIV infection rates, the highest in Western Europe, sparked alarm among the conservative public in the late 1980s and early 1990s, when up to 1,000 drug users gathered daily in Zurich's infamous Platzspitz park, dubbed "needle park."

"We had to change perspective and introduce the notion of public health. We extended a friendly hand to drug addicts and brought them out of the shadows," Ruth Dreifuss, a former Swiss president and interior minister (1993-2002), told a briefing.

Swiss authorities authorized experiments such as syringe exchange programs and safe injection rooms offering a shower, bed and hygienic conditions under medical supervision, said Dreifuss, who led the campaign to reform narcotic drug policy.

**HIV, death rates slashed**

Some 70 percent of the 20,000-30,000 opiate or cocaine users in Switzerland now receive treatment, one of the highest rates globally, said Dr. Ambros Uchtenhagen, who helped pioneer heroin substitution and chairs the Research Institute for Public Health and Addiction at Zurich University.

"The number of drug injectors with HIV has been reduced by over 50 percent in 10 years. Overdose mortality among injectors has been reduced by over 50 percent in the decade," he said. "Delinquency related to drugs has been reduced enormously."

Family doctors now prescribe about 60 percent of opiate substitution treatment in Switzerland and the Internet was vital in informing users about access to treatment, Uchtenhagen added. "I'm really impressed with the policies Switzerland has put in place, which are based on sound science and grounded in good global health policies and human rights," said Dr. Michel Kazatchkine, executive director of the Global Fund to Fight AIDS, TB and Malaria. "Switzerland is clearly a pioneer."

Up to 10 percent of all new HIV infections worldwide every year occur through injecting drug use, he said. An estimated 3 million of the 33.4 million people living with the HIV virus inject drugs, he said. "So it is a huge problem."

The AIDS epidemic is spreading faster in the Eastern Europe and Central Asia region than anywhere else, led by drug users, according to Kazatchkine. "We are still facing huge societal, political and cultural resistance to implementing evidence-based policies for intravenous drug uses," he said.

He said Russia, home to nearly 1 million people living with HIV, more than half of them drug-users, was especially reluctant to abandon its drugs policy based on law and order. "Russia is totally closed to the idea, it is impossible to open a dialogue," Kazatchkine said.

**Researchers Shed Light on HIV Gag Protein Required for Viral Assembly**

**SUMMARY:** A novel research method has enabled researchers to learn more about the structure and function of a key HIV protein known as Gag that plays a critical role in assembling new viral particles, according to a report in the *October 20, 2010 issue of Biophysical Journal*. The new artificial cell membrane technique will also allow scientists to examine other types of membrane proteins.

Below is the text of a press release issued by the National Institute of Standards and Technology describing the study findings:

**New Look at Multitalented Protein Sheds Light on Mysteries of HIV**
New insights into the human immunodeficiency virus (HIV) infection process, which leads to acquired immunodeficiency syndrome (AIDS), may now be possible through a research method recently developed in part at the National Institute of Standards and Technology (NIST), where scientists have glimpsed an important protein molecule's behavior with unprecedented clarity.

The HIV protein, known as Gag, plays several critical roles in the assembly of the human immunodeficiency virus in a host cell, but persistent difficulties with imaging Gag in a lab setting have stymied researchers' efforts to study how it functions.

"A better understanding of Gag's behavior might allow researchers to develop antiviral drugs that target the HIV assembly process, which remains unassailed by medical science," says Hirsh Nanda, a postdoctoral researcher at the NIST Center for Neutron Research (NCNR) and a member of the multi-institutional research team. "Our method might reveal how to inhibit new viruses as they grow."

The Gag molecule is a microscopic gymnast. At different stages during HIV assembly, the protein twists itself into several different shapes inside a host cell. One shape, or conformation, helps it to drag a piece of HIV genetic material toward the cell membrane, where the viral particles grow. Gag's opposite end becomes anchored there, stretching the protein into a rod-like conformation that eventually helps form a barrier surrounding the infectious genes in the finished virus. But while scientists have been aware for years that Gag appears to play several roles in HIV assembly, the specifics have remained mysterious.

The research team potentially solved this problem by creating an artificial cell membrane where Gag can show off its gymnastic prowess for the neutron probes at the NCNR. The center includes a variety of instruments specifically designed to observe large organic molecules like proteins.

"We were able to mimic the different stages of the virus's development, and look at what Gagg's conformation was at these various stages," Nanda says. "We saw conformations that had never been seen before."

Nanda describes the team's first paper on the subject as an important first step in describing their observational method, which was a joint effort between NIST, the National Cancer Institute and Carnegie-Mellon University. They plan another paper detailing what the method has revealed about HIV.

"Our efforts have not yet shown us how many steps are involved in Gag's work assembling an HIV particle, but at least we can see what it looks like in each major interaction that likely occurs in the cell during assembly," Nanda says. "It may allow us to characterize them for the first time."

Nanda says that their technique will also allow scientists to examine large classes of membrane proteins, which like Gag are notoriously hard to examine. 10/26/10

Reference

Reduction of Latent HIV Reservoir Does Not Prevent Viral Rebound after Stopping Antiretroviral Therapy

**SUMMARY:** Long-term antiretroviral therapy (ART) started during primary HIV infection can reduce plasma HIV RNA to an undetectable level and HIV proviral DNA in resting CD4 T-cells to an extremely low level—as few as 1 per 1.7 billion cells, researchers from the National Institutes of Health reported in the October 19, 2010 advance online edition of AIDS. Nevertheless, viral replication still resumes and viral load rebounds if ART is interrupted, even after 10 years on suppressive treatment.
By Liz Highleyman

The idea of curing HIV—either eradicating the virus from the body or achieving a "functional cure" that allows cessation of treatment—has recently received renewed attention.

Soon after the advent of effective combination therapy, some researchers suggested that people who start ART during primary HIV infection—the first 6 months or so after exposure—might be able to completely eliminate the virus.

Before long, however, researchers determined that integrated HIV genetic material, known as proviral DNA, remains hidden in a "reservoir" of resting memory CD4 T-cells—and possibly other types of cells as well—where it is invisible to the immune system and out of reach of antiretroviral drugs.

A team led by Tae-Wook Chun and Anthony Fauci at the National Institute of Allergy and Infectious Diseases (NIAID) has carried out some of the key studies in this area. In the mid-1990s they started treating a small cohort of patients whose HIV infection was detected very early.

Based on the half-life of latently infected CD4 T-cells and the rate at which plasma HIV levels decay, the researchers suggested that people who start treatment during primary infection might be able to eliminate all virus in resting CD4 cells with prolonged ART, estimated at 7.7 years. Others were skeptical, however, arguing that the reservoir of latent cells harboring infectious HIV might never reach zero.

Chun confirmed these misgivings in a presentation this summer at an International AIDS Society workshop preceding the International AIDS Conference in Vienna ("Towards a Cure: HIV Reservoirs and Strategies to Control Them"); this was followed by the more detailed report in the journal AIDS.

The researchers reported long-term results from 9 members of the cohort who started ART during the first 6 months after infection and 35 patients who started during chronic infection. By now, study participants had maintained plasma viral load suppression (< 50 copies/mL) for a decade, with no "blips" or transient increases.

The authors assessed the size of the HIV reservoir in resting CD4 T-cells. To do so, they collected peripheral blood mononuclear cells (PBMCs) using leukapheresis, a procedure in which blood is withdrawn, PBMCs are removed, and the blood is returned to the patient. They first used a PCR assay to measure HIV proviral DNA in purified T-cells, with a limit of detection of 2.6 copies/µg. They then used a high-input co-culture assay to look for replication-competent virus in a larger population of cells.

**Results**

- Patients who started ART during primary infection had significantly less HIV DNA in resting CD4 T-cells than those treated later (median 4.6 vs 949.4 copies per 1,000,000 cells).
- 4 out of 9 patients in the early treatment group (44.4%) and 4 out of 35 in the later treatment group (11.4%) had no measurable proviral DNA according to PCR testing.
- High-input co-culture testing detected infectious virus in CD4 T-cells from 8 early treatment patients with undetectable proviral DNA by PCR.
- One early-treated individual on ART for 10.5 years had a very small cellular HIV reservoir, estimated at 0.00064 infected cell per million, or 1 per 1.7 billion resting CD4 cells.
- This man also had undetectable HIV DNA in a sigmoid colon biopsy sample; in contrast, 1 late-treated individual with undetectable proviral DNA in peripheral blood cells also underwent gut biopsy, showing readily detectable HIV DNA.
- The individual with the very small reservoir agreed to a treatment interruption, but experienced viral rebound 50 days after ART discontinuation.

Based on these findings, the researchers concluded, "Our data suggest that a significant reduction in the size of viral reservoirs may be achievable in selected individuals who initiate standard ART early in infection."

"[T]he present study clearly demonstrated that the combination of early initiation of ART, an extended duration of therapy, and a profoundly low HIV burden in CD4+ T-cells did not eradicate HIV, nor did it inevitably suppress the re-emergence of plasma viremia," they elaborated in their discussion. "[H]owever, it did lead to a longer period (50 days) of aviremia compared to previous studies (average 9 days) after cessation of antiretroviral drugs."

These findings "suggest that the vast majority of, if not all, infected individuals receiving ART will experience plasma viral rebound regardless of the level of HIV in their CD4+ T-cell compartment at the time of discontinuation of ART," they concluded. "[G]iven re-emergence of plasma viremia in an
individual with an extraordinarily low viral burden, therapeutic strategies aimed at specifically targeting these extremely rare HIV-infected cells with novel interventions may be necessary in order to achieve eradication of virus." 10/26/10

Reference
TW Chun, JS Justement, D Murray, and others. Rebound of plasma viremia following cessation of antiretroviral therapy despite profoundly low levels of HIV reservoir: implications for eradication. AIDS (Abstract). October 19, 2010 (Epub ahead of print).

Bivalent Oral Polio Vaccine Produces Better Immune Response Than Trivalent Vaccine, Study Says
The bivalent oral polio vaccine (bOPV) was found to induce a "significantly higher immune response" than the existing trivalent oral polio vaccine (tOPV), according to a study published on Tuesday in the journal Lancet, Reuters reports (Kelland, 10/26).

The bOPV produced a "similar immune response to the monovalent vaccine," according to a Lancet press release. Though the tOPV targets all polio strains, bOPV targets types 1 and 3, which persist in "parts of the polio-endemic countries of Afghanistan, Pakistan, India, and Nigeria," the press release states (10/25).

For the study, experts from the WHO and India gave either the bOPV or existing vaccines to 830 newborn babies at three medical centers in India, Agence France-Presse reports (10/26). Vaccines were given after birth and then 30 days later, Reuters writes. "Blood samples were taken before vaccination and after the first and second doses to measure rises in antibody levels,” the news service reports (10/26). Researchers found that after two doses of either the mOPV1 or bOPV, "approximately 90% of babies developed immunity to type 1 virus, compared with 69% after tOPV. The second dose induced immunity to type 3 virus in 84% of recipients of mOPV3, 74% of bOPV, and 52% of tOPV," the press release notes (10/25).

The WHO’s Roland Sutter, who led the study, said, "This (new) vaccine could get us over the top and get us to the finish line for eradication," the BBC reports. "The dramatic drop in the number of polio cases in India and Nigeria is attributable to the new vaccine and better coverage during immunization campaigns," he said (Lichtarowicz, 10/25). The study received most of its funding from the GAVI Alliance, the press release states (10/25).

In a related Lancet commentary, "Nigel Crawford and Jim Buttery from the Murdoch Children’s Research Institute in Melbourne, Australia, said the potential effectiveness of the bivalent vaccine was already being shown in India where it is being used on a large scale. Latest polo data show just 32 cases so far this year, compared with 260 in 2009, they wrote," according to Reuters. They also pointed out that the global economic situation has led to a significant funding shortfall, which could threaten the goal of polio eradication.

"The plan of action for polio eradication – with bOPV as the centrepiece – is only 50 percent funded for 2010-12,’ they wrote. They described the potential of the new bivalent vaccine as 'an important step forward' but said ‘a final concerted effort, both locally and worldwide, is required’ to succeed in finally eradicating the virus,” according to Reuters (10/26).

U.N. Foundation Leaders Note Polio Vaccine Partnership Successes In Nigeria
U.N. Foundation Founder and Chairman Ted Turner was in Nigeria on Monday, noting the country’s success in efforts to eliminate polio, the AFP reports (10/25).

Turner is in the country along with U.N. Foundation President Timothy Wirth and U.N. Foundation Board Member Andrew Young "to meet with government and community leaders to learn firsthand about the power of public-private partnerships aimed at improving children's health," according to a U.N. Foundation press release. The visit comes at the end of a week-long board meeting in Africa (10/25).

"The foundation said in a statement that recent progress in Nigeria is proof that vaccines are key to eradicating polio and reducing measles worldwide. 'Working together, I know we can finish the job on polio,’ Turner said after talks with key government officials and traditional rulers, particularly in northern Nigeria, where the threat is more pronounced," AFP writes (10/25).

Turner said the public-private partnerships that have been instrumental in fighting polio in Nigeria could be used as a model to deal with other health challenges. "With support from leaders like the Sultan of Sokoto, we are on the verge of achieving the first great humanitarian victory of the 21st century – the complete elimination of a disease that once afflicted millions. By building on the success of partnerships like these, we can eliminate measles and protect children from other vaccine-preventable diseases to achieve the Millennium Development Goals (MDGs)," he said, the press release notes. "Last year Nigeria
reduced cases of polio by 98 percent with only eight cases confirmed in 2010, as compared to nearly 400 in the fall of 2009," according to the release (10/25).

**A new player in the innate immunity game?**

**Findings could signal paradigm shift in understanding of host response to viral infection**

Scientists have demonstrated for the first time that a certain class of RNA (known as long non-protein-coding RNA [lncRNA]) are involved in the host response to viral infection. These findings, published today in the online journal *mBio*, could greatly change the way scientists look at the body's response to viral infection.

"To our knowledge, our study is the first to use comprehensive deep-sequencing technology to clearly demonstrate that lncRNAs are involved in the host response to viral infection and innate immunity," says Michael Katze of the University of Washington, and STRIDE (Center for Systems and Translational Research on Infectious Disease) in Seattle, a lead researcher on the study.

RNA molecules are transcribed from the DNA and help translate the genetic code. They often serve as templates for building compounds the body needs to function including proteins.

Many studies of how animals' cells respond to viral infections focus only on protein-coding genes, which assemble germ-fighting or inflammation-inducing proteins used by the immune system. However there is growing evidence that thousands of RNAs are transcribed that do not code for proteins.

"The relevance of lncRNAs to viral infections has not been systematically studied, in part because these ncRNAs have not been easily accessible with typically available technologies," says Katze. "With the advent of next-generation sequencing technologies, whole transcriptome analysis of the host response, including ncRNAs, is now possible."

The library of RNA transcripts inside of a cell is called its transcriptome and is a reflection of gene activity. *Many different RNAs can be read from a single gene. Therefore a transcriptome contains much more complex instructions than would seem possible from the DNA code.*

Unlike the genome, the transcriptome varies in different types of cells in the body and in accordance with ever-changing conditions inside and outside the cell.

Katze and his research team used highly advanced technologies, such as next generation sequencing (NGS), to perform a whole transcriptome analysis of the host response to severe acute respiratory syndrome coronavirus (SARS-CoV) and influenza infection in four strains of mice, some more susceptible to the viruses than others. Using this deep-sequencing technology, the researchers analyzed whole transcriptomes in cells from infected lung samples collected from the mice.

The researchers observed that virus infection triggered activity in about 500 lncRNAs transcribed from known locations on the genome and about 1,000 from previously unspecified genomic regions. They were also interested to discover, through studies of subsets of the lncRNAs and genomic regions, that most of these were similarly regulated in response influenza virus infection. This profile contained unique "signatures" of lncRNA activity and these signatures were associated with lethal infection.

"These findings represent the first discovery of the widespread differential expression of long ncRNAs in response to virus infection and suggest that ncRNAs are involved in regulating the host response, including innate immunity," says Katze. "In the future, it is likely that a detailed knowledge of ncRNA regulation and function will be necessary for a full understanding of viral pathogenesis."

**'Reaper' Protein Strikes at Mitochondria to Kill Cells**

ScienceDaily (Oct. 20, 2010) — Our cells live ever on the verge of suicide, requiring the close attention of a team of molecules to prevent the cells from pulling the trigger. This self-destructive tendency can be a very good thing, as when dangerous precancerous cells are permitted to kill themselves, but it can also go horribly wrong, destroying brain cells that store memories, for instance.

Rockefeller University scientists are parsing this perilous arrangement in ever finer detail in hopes that understanding the basic mechanisms of programmed cell death, or apoptosis, will enable them eventually to manipulate the process to kill the cells we want to kill and protect the ones we don't.

In experiments published last month in the *Journal of Cell Biology*, researchers led by postdoctoral associate Cristinel Sandu in Hermann Steller's Strang Laboratory of Apoptosis and Cancer Biology drilled down on a protein aptly named Reaper, which was first described in a 1994 paper by Steller in *Science*. Under the right conditions, Reaper interferes with molecules called inhibitor of apoptosis proteins (IAPs),
which prevent the cell from irrevocably initiating its autodestruct sequence. By inhibiting these inhibitors, Reaper essentially takes the brakes off the process of apoptosis, pronouncing a cell's death sentence. Other molecules called caspases then carry that sentence out.

"Like the grim reaper, Reaper is an announcer of death, but not the executioner," says Steller, who is also a Howard Hughes Medical Institute investigator. "It's like the key that starts the engine."

Reaper and the other *Drosophila* IAP antagonists Hid and Grim are known to trigger apoptosis in flies, and related proteins serve a similar function in humans and other mammals. But exactly how and where Reaper initiates apoptosis has not been well understood. Sandu and colleagues bred genetically modified strains of flies that expressed variations on the Reaper protein specifically in flies' eyes. This allowed them to assess the contribution of individual protein motifs to Reaper's apoptosis inducing powers, and what they found was that a particular helical domain was crucial for the formation of Reaper complexes, and could be modified to be even more powerful than the regular protein. The more deadly Reaper variants were obvious by the damage caused to the flies' eyes.

In a series of biochemical experiments, the researchers also found that Reaper must travel to the mitochondria, the cell's energy factories, to effectively deliver its death sentence, and that to get there, it must hitch a ride on the Hid protein, with which it interacts. By tagging Hid and Reaper fluorescently, Sandu could visualize Hid and Reaper acting in a complex and gathering at the membrane of the mitochondria. When Reaper was engineered to go directly to the mitochondrial membrane, it resulted in a molecule that is far superior at triggering cell death than regular Reaper. Further experiments suggested that in a complex with Hid, Reaper is protected from degradation as the cells began to die.

"So now we have Hid and Reaper working very closely together," Sandu says. "And the localization to the mitochondria is crucial to the initiation of apoptosis." Drugs that mimic a small part of the function of Reaper are already in clinical trials. The discovery of a way to make Reaper a much better killer, namely by targeting it directly to the mitochondria, provides new avenues to explore for improving cancer therapies. "Adding this element that takes Reaper directly to the mitochondria is not something people would have thought of before this," Steller says.

**Journal Reference:**

**Immuine Cells Deploy Traps to Catch and Kill Pathogens**

ScienceDaily (Oct. 26, 2010) — A new study reveals that two enzymes help immune cells deploy pathogen-killing traps by unraveling and using the chromatin (DNA and its associated proteins) contained in the cells' nuclei to form defensive webs.

The study appears online on October 25 in *The Journal of Cell Biology*.

Neutrophils, the most common type of white blood cells, are difficult to study because they live for only about six hours. So Arturo Zychlinsky and colleagues, from the Max Planck Institute for Infection Biology in Berlin, created a cell-free system that includes neutrophil nuclei and dollops of cytoplasm from the cells.

They found that two enzymes stashed in cytoplasmic granules enter the nucleus and join forces to unwind the chromatin and form neutrophil extracellular traps (NETs), webs of chromatin that catch and kill pathogens. The first to make the move is neutrophil elastase (NE), which promotes chromosome decondensation by breaking down two "histone" proteins that help keep chromatin tightly packaged in the nucleus.

Later in the process, myeloperoxidase (MPO) arrives at the nucleus to help NE unravel the chromatin. Exactly how MPO performs its task remains unclear, as its catalytic activity isn’t required to decondense chromatin.

The researchers confirmed NE's importance for NET formation by exposing mice to Klebsiella pneumoniae bacteria. Neutrophils hustled to the lungs in control mice and in animals lacking NE. But neutrophils from the mice missing NE couldn’t produce NETs to snare the bugs.

An important question to answer now, the researchers say, is how NE and MPO travel to the nucleus. The granules could merge with the nuclear membrane directly or burst and free the enzymes into the cytoplasm, from where they subsequently move to the nucleus.

**Journal Reference:**
Molecular Guardian of Cell's RNA Identified

Pre-mRNA is the direct transcript of a gene, but needs to be processed to form mRNA, including splicing of introns and joining of exons, as well as cleavage/polyadenylation at the end of the transcript. (Credit: The Dreyfuss Laboratory; Penn Medicine)

ScienceDaily (Oct. 26, 2010) — When most genes are transcribed, the nascent RNAs they produce are not quite ready to be translated into proteins—they have to be processed first. One of those processes is called splicing, a mechanism by which non-coding gene sequences are removed and the remaining protein-coding sequences are joined together to form a final, mature messenger RNA (mRNA), which contains the recipe for making a protein.

For years, researchers have understood the roles played by the molecular machines that carry out the splicing process. But, as it turns out, one of those familiar components plays a new, and altogether unexpected role.

As senior author Gideon Dreyfuss, PhD, the Isaac Norris Professor of Biochemistry and Biophysics at the University of Pennsylvania School of Medicine and colleagues report in Nature, one of the splicing machinery's components called U1 has a second, equally important role in gene expression: To enable gene sequences to be read out into their RNA transcripts in their entirety, rather than have that process prematurely stopped. Dreyfuss is also a Howard Hughes Medical Institute Investigator.

The researchers revealed an unexpected function for U1 in protecting mRNA transcripts from premature termination in addition to and independent of its role in splicing.

As Dreyfuss puts it, "U1 is a guardian of the transcriptome." The transcriptome is the set of all RNA molecules in one cell.
U1 is one of a collection of RNA-protein complexes, called snRNPs, that recognize splicing junctions, excise non-coding gene sequences called introns, and join the remaining coding sequences called exons together. The Dreyfuss team previously showed that loss of SMN, a protein that helps assemble snRNPs and is deficient in individuals with the common neurodegenerative disease spinal muscular atrophy (SMA), results in altered snRNP levels and abnormal splicing.

SMN deficiency affects all snRNPs to one degree or another. The Dreyfuss team wanted to find out what would happen if just one snRNP was missing. They started with U1.

The team’s expectation was that they would detect an increase in unspliced RNA transcripts, and indeed they saw evidence of that. But, to their surprise, the majority of the genes produced a very different and striking result. Their transcripts terminated prematurely and abruptly, generally within a relatively short distance from the transcription start site of the gene.

When they sequenced the ends of the resulting truncated RNAs, they found that they had been prematurely cleaved and tagged with a long string of nucleotide building blocks called adenine. This string is a hallmark of a process called cleavage-and-polyadenylation, which normally occurs at the end of a gene’s RNA transcript. The lack of U1 was causing the cleavage/polyadenylation machinery to kick into gear early.

The implication, Dreyfuss says, is that U1’s normal role, in addition to splicing, is to keep the cleavage/polyadenylation machinery in check until the RNA polymerase enzyme that synthesizes the transcript reaches its finish line. The researchers propose a model in which U1 binds throughout the nascent RNA transcripts, stymieing the cleavage/polyadenylation machinery that tags along with the moving polymerase complex. This in turn protects the many potential polyadenylation signals encountered along the way, and could explain the relative abundance of U1 in cells compared to other snRNPs. The additional U1 corresponds to the greater amount needed for its additional function.

“The transcripts are under constant threat from the cleavage/polyadenylation machinery,” Dreyfuss explains. “This machinery doesn’t patiently wait for the transcript to reach the end of the gene; rather, the nascent RNA transcripts are subject to becoming attacked by this machinery. It’s a constant danger they face, and the U1 snRNP suppresses it.”

It is, he says, "a novel role" for U1, and a critical component for correctly making mRNA. "It is essential for the integrity of the transcriptome, the landscape of all mRNA molecules in the cell," he concludes.

Journal References:

1000 Genomes Project publishes analysis of completed pilot phase

Small genetic differences between individuals help explain why some people have a higher risk than others for developing illnesses such as diabetes or cancer. Today in the journal Nature, the 1000 Genomes Project, an international public-private consortium, published the most comprehensive map of these genetic differences, called variations, estimated to contain approximately 95 percent of the genetic variation of any person on Earth.

Researchers produced the map using next-generation DNA sequencing technologies to systematically characterize human genetic variation in 180 people in three pilot studies. Moreover, the full scale-up from the pilots is already under way, with data already collected from more than 1,000 people.

"The pilot studies of the 1000 Genomes Project laid a critical foundation for studying human genetic variation," said Richard Durbin, Ph.D., of the Wellcome Trust Sanger Institute and co-chair of the consortium. "These proof-of-principle studies are enabling consortium scientists to create a comprehensive, publicly available map of genetic variation that will ultimately collect sequence from 2,500 people from multiple populations worldwide and underpin future genetics research."

Genetic variation between people refers to differences in the order of the chemical units — called bases — that make up DNA in the human genome. These differences can be as small as a single base being replaced by a different one — which is called a single nucleotide polymorphism (abbreviated SNP) — or is as large as whole sections of a chromosome being duplicated or relocated to another place in the genome. Some of these variations are common in the population and some are rare. By comparing many
individuals to one another and by comparing one population to other populations, researchers can create a map of all types of genetic variation.

The 1000 Genomes Project’s aim is to provide a comprehensive public resource that supports researchers aiming to study all types of genetic variation that might cause human disease. The project’s approach goes beyond previous efforts in capturing and integrating data on all types of variation, and by studying samples from numerous human populations with informed consent allowing free data release without restriction on use. Already, these data have been used in studies of the genetic basis for disease.

"By making data from the project freely available to the research community, it is already impacting research for both rare and common diseases," said David Altshuler, M.D., Ph.D., Deputy Director of the Broad Institute of Harvard and MIT, and a co-chair of the project. "Biotech companies have developed genotyping products to test common variants from the project for a role in disease. Every published study using next-generation sequencing to find rare disease mutations, and those in cancer, used project data to filter out variants that might obscure their results."

The project has studied populations with European, West African and East Asian ancestry. Using the newest technologies for sequencing DNA, the project’s nine centers sequenced the whole genome of 179 people and the protein-coding genes of 697 people. Each region was sequenced several times, so that more than 4.5 terabases (4.5 million million base letters) of DNA sequence were collected. A consortium involving academic centers on multiple continents and technology companies that developed and sell the sequencing equipment carried out the work.

To process these data required many technical and computational innovations, including standardized ways to organize, store, analyze and share DNA sequencing data. Launched in 2008, the 1000 Genomes Project started with three pilot projects to develop, evaluate and compare strategies for producing a catalogue of genetic variations. Funded through numerous mechanisms by foundations and national governments, the 1000 Genome Project will cost some $120 million over five years, ending in 2012.

When the work began, sequencing was very expensive, so the project began with two approaches aimed at increasing efficiency: One strategy, called "low-pass", combines partial data from many people; the second, only focused on the part of the genome that encodes protein-coding genes. By comparing these strategies to "gold standard" data produced at great completeness and accuracy, the project was able to show that both the alternative approaches work well and have complementary strengths. Researchers will use both strategies in the full-scale project because, although sequencing costs have decreased, it is still relatively expensive.

"We have shown for the first time that a new approach to sequencing — low coverage of many samples — works efficiently and well," said Gil McVean, Ph.D., Professor of Statistical Genetics at the University of Oxford. "This proof of principle is now being applied not only in the 1000 Genomes Project, but in disease research, as well."

The resulting map of human genetic variation includes about 15 million SNPs, 1 million short insertion/deletion changes, and more than 20,000 structural variations. Many of the genetic variants had previously been identified, but more than half were new. The project’s database contains more than 95 percent of the currently measurable variants found in any individual, and continuing work will eventually identify more than 99 percent of human variants.

Richard Gibbs, Ph.D., director of the Human Genome Sequencing Center at the Baylor College of Medicine (one of the project’s sequencing centers) said, "What really excites me about this project is the focus on identifying variants in the protein-coding genes that have functional consequences. These will be extremely useful for studies of disease and evolution."

The improved map produced some surprises. For example, the researchers discovered that on average, each person carries between 250 and 300 genetic changes that would cause a gene to stop working normally, and that each person also carried between 50 and 100 genetic variations that had previously been associated with an inherited disease. No human carries a perfect set of genes. Fortunately, because each person carries at least two copies of every gene, individuals likely remain healthy, even while carrying these defective genes, if the second copy works normally.

In addition to looking at variants that are shared between many people, the researchers also investigated in detail the genomes of six people: two mother-father-daughter nuclear families. By finding new variants present in the daughter but not the parents, the team was able to observe the precise rate of mutations in humans, showing that each person has approximately 60 new mutations that are not in either parent.
With the completion of the pilot phase, the 1000 Genomes Project has moved into full-scale studies in which 2,500 samples from 27 populations will be studied over the next two years. Data from the pilot studies and the full-scale project are freely available on the project web site, www.1000genomes.org.

Researchers studying specific illnesses, such as heart disease or cancer, use maps of genetic variation to help them identify genetic changes that may contribute to the illnesses. Over the last five years, the first generation of such studies (called genome-wide association studies or GWAS) have been based on an earlier map of genetic variation called the HapMap. Built using older technology, HapMap lacks the completeness and detail of the 1000 Genomes Project.

"The 1000 Genomes Project map fills in the gaps between the HapMap landmarks, helping researchers identify all candidate genes in a region associated with a disease," said Lisa Brooks, Ph.D., program director for genetic variation at the National Human Genome Research Institute, a part of the National Institutes of Health. "Once a disease-associated region of the genome is identified, experimental studies must be done to identify which variants, genes, and regulatory elements cause the increased disease risk. With the new map, researchers can just look up all the candidate genes and almost all of the variants in the database, saving them many steps in finding the causes.”

**Homosexuals Contribute 30% Of New Hiv Infections In Kenya – NASCOP**

Kenya’s National Aids and Sexually Transmitted Diseases Control Program (NASCOP) is considering supplying free syringes to drug injecting users and incorporating gay and lesbian HIV mitigation programmes in its National Control Aids Plans. This follows a revelation by NASCOP that homosexuals and drug users contribute to 30% of new HIV infections in the country.

Earlier this month, church leaders condemned cabinet minister, Eshter Murugi, after she called for recognition of homosexuals in the fight against the spread of HIV and AIDS.

Meanwhile Kenya’s national women’s movement Maendeleo ya Wanawake has challenged minorities and marginalized groups to stand up and vie for political leadership created under the new constitution.

Its national secretary general Alice Kirambi said the time has come for the minorities to fight for parliamentary, Senate and governor seats.

“These are legislative and governance offices where laws are enacted and decisions made and this time round we want the minorities and the marginalized to come on board so that they become decision makers on issues that affect them, particularly on human rights and gender”, Kirambi explained.

**Eve of an HIV Epidemic in Romania**


Eastern Europe and central Asia have the world’s fastest-growing HIV epidemic, and experts say injecting drug use largely is to blame. Regional HIV prevalence has grown 66 percent since 2001 and now stands at 1.5 million people, according to UNAIDS. “The only difference between eastern Europe and Africa is time,” said Shona Schonning, an activist with the Lithuania-based Eurasian Harm Reduction Network.

Romania, however, has been an exception. Its epidemic is unusual in that most HIV patients were infected in the 1980s through an ill-conceived and unsanitary blood transfusion program that targeted anemia in the nation’s orphanages. In 2001, a favorable deal with drug makers helped Romania become the first eastern European nation to provide universal HIV medications. Needle-exchange programs (NEPs) run by non-governmental organizations last year distributed more than 1.6 million syringes to 7,500 addicts, helping to hold HIV prevalence among drug injectors to just 1 percent—the lowest figure in eastern Europe. Now, however, that progress is in jeopardy.

The World Bank no longer classifies Romania as a developing nation, meaning it is ineligible for the international grants that fund its NEPs. Since June, UNICEF, the Open Society Institute and the Global Fund to Fight AIDS, TB and Malaria all have pulled funds from Romania’s HIV efforts. “Where you don’t provide interventions for drug injectors, there’s a potential for the epidemic to rage out of control,” said Martin Christopher Donoghoe, the World Health Organization’s HIV/AIDS project manager for Europe.

Romania’s government, coping with an economy that shrunk 7 percent last year, is unlikely to pick up the slack. Some, however, hold out hope.

Early in the decade, Romania “was the model for the region,” said Eduard Petrescu, UNAIDS country coordinator. “I hope in two or three years it will be seen as the model of how to deal with HIV/AIDS during an economic crisis.”
Study Reveals Risky Sex Behavior Among NYC Teens
Almost one in 10 sexually active New York City high school students have had at least one same-sex partner, and males with both same-sex and opposite-sex partners reported the lowest levels of condom use, according to a new analysis of the 2005-2007 New York City Youth Risk Behavior Surveys. The city YRBS was administered to a representative sample of city high schools.

Of 17,220 students surveyed, 7,261 reported having had sexual intercourse. Among them, the proportion of males and females who reported only same-sex partners was identical, 3.2 percent. Of sexually active teens, 9.3 percent reported having at least one same-sex partner. Fewer males than females reported partners of both genders (3.7 percent vs. 8.7 percent; P<0.001). Among teens with at least one same-sex partner, 38.9 self-identified as “heterosexual or straight.” Of males, 93.1 percent reported only opposite-sex partners, compared with 88.1 percent of females.

Participants reporting partners of both genders also indicated higher-than-average rates of risky sex, such as not using a condom, and higher rates of partner violence and forced sex. Of girls with partners of both genders, 35.8 percent experienced dating violence in the previous year, as did 34.8 percent of males with male and female partners.

Condom use during most recent sex was reported by 79.8 percent of males with only female partners, compared with 62.3 percent of males with only male partners and 44.1 percent of males with partners of both sexes.

“It has been shown in the literature that students who have both male and female partners have a lot of adverse health problems,” said Dr. Susan Blank, assistant commissioner of the city health department and head of its STD prevention efforts. The data are a reminder that “our public health prevention messages really need to look at behavior, not identity,” she said.


High hepatitis C mortality and low clearance rates in HIV/HCV-co-infected patients in France
Michael Carter
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Mortality rates are high among French patients co-infected with HIV and hepatitis C, investigators report in BMC Infectious Diseases. Over 40% of deaths were directly attributable to hepatitis C.

Only a fifth of patients with hepatitis C genotype 1 and 36% of those with genotype 4 treated since 2005 had a successful response to treatment, a finding broadly in line with the results of clinical trials in coinfected people. Only 21% of patients in the French cohort had HCV genotypes 2 or 3, which have proved more likely to respond to treatment.

A low overall success rate was seen in individuals who received a second course of treatment for hepatitis C.

However, treatment for depression not only improved mood but also fatigue and other aspects of health.

Approximately a quarter of HIV-positive patients in France are co-infected with hepatitis C. Investigators wanted to gain a better understanding of these patients, and in 2005 established ANRS CO 13 HEPAVIH cohort.

The investigators describe the cohort as “a unique nation-wide collaboration of HIV treatment, infectious diseases, internal medicine and hepatology centres.”

Between 2006 and 2008 a total of 1175 adults were recruited to the cohort. All were HIV-positive, 1048 had chronic hepatitis C infection and 127 had had a sustained response to hepatitis C therapy. The patients’ median age was 45 years, 70% were men, their median CD4 cell count was 442 cells/mm³ and 68% had an undetectable HIV viral load.

Most of the patients (71%) were infected with hepatitis C through injecting drug use and the median time since diagnosis of hepatitis C was ten years. The median hepatitis C viral load was 6.2 logU/ml.

A variety of tests were used to assess the extent of liver damage caused by hepatitis C. The proportion of patients diagnosed with cirrhosis varied according to which test was used.

FibroTest detected cirrhosis in 46% of patients, FibroScan in 30% and a liver biopsy in 27%.

Nevertheless, all the tests had a high positive predictive value for cirrhosis diagnosis.
At the time of enrolment to the cohort, 72% of patients were taking antiretroviral therapy. The majority of patients (58%) were taking a combination of drugs based on a ritonavir-boosted protease inhibitor.

Overall, 51% of patients had received hepatitis C therapy. Most 35% received this treatment before they entered the cohort.

Outcome data were available for 127 patients who had received hepatitis C treatment after entering the cohort.

A total of 32% had a sustained virologic response. The clearance rate was 34% for those taking anti-hepatitis C drugs for the first time, and fell to 27% for individuals taking a second course of therapy.

Outcomes were also analysed according to hepatitis C genotype. Only 20% of patients infected with genotype 1 had a successful response to therapy, and 36% of those with genotype 4 cleared the infection.

By January 2010, a total of 13 new cases of cirrhosis had been diagnosed. All were in patients with chronic hepatitis C. There were nine new cases of liver cancer, three of which were in patients who had had a sustained response to therapy with anti-hepatitis C drugs.

There were 49 deaths, and 41% were attributed to hepatitis C.

The investigators calculated that the rate of severe hepatitis C-related events was 2 per 100 person years of follow-up.

Event rates were notably higher in patients with cirrhosis (7 vs. 0.35 per 100 person years). The investigators note that this was expected, but nevertheless emphasised the importance of accurately diagnosing cirrhosis. All three types of tests detected over 99% of cases of cirrhosis.

A low baseline CD4 cell count (below 200 cells/mm$^3$) also significantly increased the risk of a serious hepatitis C-related outcome (5.5 vs. 1.4 per 100 person years; $p = 0.002$). Patients co-infected with hepatitis C are especially recommended to start antiretroviral therapy when their CD4 cell count is around 350 cells/mm$^3$.

Using information gathered from questionnaires completed by the patients, the investigators found that treating depression not only improved mood, but also had an impact on fatigue, as well as boosting cognitive, physical and social functioning.

The researchers conclude that cohorts such as theirs “will be critical to address future clinical and public health questions of chronic diseases of infectious origin”.

Reference

Manitoba judge overturns sex-assault convictions in HIV-nondisclosure case

An HIV-positive man convicted of multiple counts of aggravated sexual assault last year had his convictions reduced from six to two by the Manitoba Court of Appeal last week.

In her 62-page decision, Justice Freda Steel found the trial judge was wrong to conclude everyone who had sexual relations with the accused was exposed to "significant risk."

In the four overturned sex assault convictions, Steel referred to medical evidence that showed the risk of exposure was low when the accused wore a condom. The judge also cited evidence that the accused’s antiretroviral therapy meant there was a "high probability" he wasn’t infectious.

The decision also stated:
"The law, with respect to aggravated sexual assault and the transmission of HIV, as developed by the Supreme Court of Canada in Cuerrier, attaches criminal liability to the failure to disclose one’s positive HIV status only when there is a ‘significant risk of serious bodily harm,’

And:
"That determination will vary depending on the scientific and medical evidence adduced in each particular case. In this case, the scientific evidence indicated that either the careful use of a condom or effective antiretroviral therapy which reduced viral loads to an undetectable level could potentially reduce the level of risk to below the legal test of ‘significant risk,’

And:
"Although the accused knew that he was HIV-positive, and despite medical warnings to the contrary, he did not disclose that condition to the complainants, who, with one exception, would not have consented if they had known he was HIV-positive... I can well understand that those complainants feel, in their opinion, that the nature and quality of the sexual act was fundamentally changed by the lack of disclosure of the risk of disease.”
Cecile Kazatchkine, spokesperson for HIV/AIDS Legal Network, says this is a legal landmark for Canadian HIV-nondisclosure cases.

"The principal issue on the appeal was whether the trial judge erred in her application of the legal test of 'significant risk of serious bodily harm' (ie significant risk of HIV transmission) in the particular circumstances of the case. The trial judge considered that even when a condom is used there is a significant risk of HIV transmission for the purpose of the criminal law and reached the same conclusion for an undetectable viral load. [The trial judge said] the risk would only be sufficiently reduced when a person has both an undetectable viral load and uses a condom,” says Kazatchkine.

Kazatchkine points to the 1998 Supreme Court of Canada's R v Cuerrier decision, which decided a poz person can be convicted of aggravated sexual assault for not disclosing his or her serostatus to sex partners before engaging in an activity representing a significant risk of HIV transmission.

"[Justice Steel] stated very clearly that the test set out in Cuerrier was not a 'no risk' test but required the presence of a significant risk. The Court further explained that 'significant risk' means something other than an ordinary risk. It means an important, serious, substantial risk. The Court of Appeal also stated that legal assessments of risk in this area should be consistent with the available medical studies and acknowledged the application of the legal test in Cuerrier must evolve to account appropriately for the development in the science of HIV treatment. As a result, the Court decided that the careful use of a condom or an undetectable viral load can reduce the level of risk below the threshold test of a significant risk,” says Kazatchkine.

While there is a fight to create consistent application of the law in nondisclosure cases, Kazatchkine says only lower Manitoba courts will be bound by this decision and it can be appealed to the Supreme Court. And while the court ruled condom use and undetectable viral load can be enough to reduce or exclude criminal liability, it does not provide certainty that use of a condom or having an undetectable viral load removes the requirement to disclose.

"The decision, limiting the scope of the criminal law to the very circumstances where the risk of HIV transmission is real, has great merit. It clearly rejects the argument that sex can never be consensual in the case of nondisclosure. The Court recognizes that this is not the law in Canada and that the criminal sanctions should be reserved for those deliberate, irresponsible or reckless individuals who do not respond to public health directives and who are truly blameworthy," says Kazatchkine.

Jason Gratl, a BC defence lawyer, defended a poz man who failed to disclose his serostatus before having unprotected sex with his boyfriend and was found not guilty May 7. While each case has its differences, he says this Manitoba case seems consistent with his case in BC.

The accused in the Manitoba case immigrated to Canada from Sudan in 2000. Originally sentenced to 14 years, his sentence will be reduced and he will be deported upon release. He is the second Winnipeg-based Sudanese immigrant to be in the news for HIV nondisclosure this year.

New Strategy to Kill Bugs—Even Those in Hiding

ScienceDaily (Oct. 29, 2010) — New strategies to apply antibiotics more effectively to hibernating bugs have been developed by researchers at the University of Hertfordshire.

In a paper, which appeared this month in the *Institute of Electrical and Electronics Engineers (IEEE) Transactions on Evolutionary Computing*, Dr Ole Steuernagel and Dr Daniel Polani from the University's Science and Technology Research Institute describe how to apply antibiotics to wipe out bacteria that form active as well as inactive subpopulations.

"One of the difficulties of applying antibiotic strategies against bugs is that some of the microbes tend to go into hibernation,” said Dr Steuernagel. "Although the medication can wipe out the active populations, it often misses the hibernating ones because they are metabolically inactive. It may not be enough just to kill off the active bacteria, the hibernating rest will ‘wake up' and reestablish themselves.”

Through use of an optimization approach called 'multiobjective optimization' that is tailored to such multifaceted scenarios, the researchers found that the best solution is to kill the microbes early and late during the therapy period, but not during the intermediate period.

"This is the first time that this approach has been used in a bug eradication scenario and our solutions should be more efficient than existing approaches to kill hibernating bugs," said Dr Steuernagel. "Current practice does not take account of persistence due to hibernation although this may well be a problem. After all, microbes which are known to hibernate include *Escherichia coli*, multiply resistant *Staphylococcus aureus* (MRSA—"superbug"), *Mycobacterium tuberculosis*, *Pseudomonas aeruginosa*."
Journal Reference: