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**Cranberry Juice Shows Promise Blocking Staph Infections**

ScienceDaily (Sep. 3, 2010) — Expanding their scope of study on the mechanisms of bacterial infection, researchers at Worcester Polytechnic Institute (WPI) have reported the surprise finding from a small clinical study that cranberry juice cocktail blocked a strain of *Staphylococcus aureus* (*S. aureus*) from beginning the process of infection.

The data was reported in a poster presentation at the American Chemical Society's national meeting in Boston on August 23, 2010, by Terri Camesano, professor of chemical engineering at WPI. "Most of our work with cranberry juice has been with *E. coli* and urinary tract infections, but we included *Staphylococcus aureus* in this study because it is a very serious health threat,” Camesano said. “This is early data, but the results are surprising.”

The virulent form of *E. coli* that Camesano studies is the primary cause of most urinary tract infections. Strains of *S. aureus* can cause a range of "staph infections" from minor skin rashes to serious bloodstream infections. One particular strain, known as Methicillin-resistant *Staphylococcus aureus*, or
MRSA, is a growing public health problem in hospitals, nursing homes, and other institutions because it doesn't respond to most antibiotics.

To cause an infection, bacteria must first adhere to a host, then gather together in colonies to form a biofilm. In the current study, Camesano recruited healthy female students at WPI to drink either cranberry juice cocktail or a placebo fluid that looked and tasted like cranberry juice. The subjects provide urine samples at prescribed intervals after drinking the juice or placebo, and those samples were incubated in petri dishes with several strains of E. coli and a single strain of S. aureus. Camesano's team stained the bacteria with a special dye, then used a spectrophotometer to measure the density of the bacterial colonies in the dishes over time. Their analysis showed that the urine samples from subjects who had recently consumed cranberry juice cocktail significantly reduced the ability of E. coli and S. aureus to form biofilms on the surface of the dishes.

"What was surprising is that Staphylococcus aureus showed the most significant results in this study," Camesano said. "We saw essentially no biofilm in the staph samples, which is very surprising because Staph aureus is usually very good at forming biofilms. That's what makes it such a health problem."

With E. coli, Camesano's focal point is the small hair-like projections known as fimbriae, which act like hooks and help the bacteria latch onto cells that line the urinary tract. Camesano has shown that exposure to cranberry juice causes the fimbriae on E. coli to curl up, blunting their ability to attach to cells. S. aureus, however, doesn't have fimbriae, so there must be other reasons why the cranberry juice affected its biofilm formation in the study. "These results do create more questions than answers," Camesano said. "We believe this is an important new area to explore, and we are now thinking about how best to proceed."

Since bacterial adhesion is required for infection, Camesano hopes that better understanding of the specific mechanisms and forces involved in biofilm formation will help inform future studies aimed at identifying potential drug targets for new antibiotics. The data may also be useful in studies aimed at engineering the surfaces of invasive medical devices like catheters to make them more resistant to bacterial adhesion.

NYTimes, September 3, 2010

H.I.V. Prevention Gel Hits Snag: Money

By CELIA W. DUGGER

JOHANNESBURG — When scientists celebrated the announcement in July that a vaginal microbicide had finally been found that significantly reduced H.I.V. infections in women, there was still a prosaic — though essential — piece of the puzzle missing: money.

Donors have not committed enough money for even one of the two studies needed to confirm a promising South African trial of the microbicide and get it into women's hands. Only about $58 million of the $100 million needed for follow-up research has been pledged, according to UnAids, the United Nations AIDS agency. Experts say shifting global health priorities and tight finances in the West are making it hard to raise the rest.

Advocates say any delay could be deadly. Most of the 22 million people infected with H.I.V. in sub-Saharan Africa are women, and about a million women on the continent are infected each year. If subsequent studies find the gel effective, women could use it to protect themselves even when men refuse to use condoms.

"We have to keep our eye on the prize," said Dr. Catherine Hankins, chief scientific adviser to UnAids. "It's in reach. We have to close the funding gap and get the gel to women."

Dozens of scientists and public health experts at a conference here last week agreed on the research needed to speed the microbicide to widespread use. They called for two more trials in southern Africa and steps to promote and distribute the vaginal gel, infused with the antiviral drug tenofovir, through family planning programs.

The original study of the gel found that women who used it before and after sex were 39 percent less likely over all to contract H.I.V. than those who used a placebo. Those who used the gel most regularly cut their odds of infection by 54 percent.

Researchers have tried for two decades to find a microbicide to fight H.I.V. transmission. So far, the American and South African governments have come up with a vast majority of the additional research money, while Britain's Department for International Development, a major supporter of microbicide research, has committed nothing.
Participants in the conference said an agency official said the British government’s priorities were shifting away from AIDS and toward maternal and child health, malaria and tuberculosis.

“H.I.V./AIDS is perceived to be very expensive research, and there's a sentiment in the U.K. that it's time to shift priorities,” said Tim Farley, a World Health Organization scientist who attended the conference.

The British agency was noncommittal in a statement, saying that future spending “will be made based on impact on poverty eradication on the ground.”

Researchers also worry that the Bill and Melinda Gates Foundation, the most important philanthropic supporter, has not committed major financing for the additional studies on the gel. Dr. Stefano Bertozzi, who heads the foundation’s AIDS programs, said the gel — with a solid study showing its effectiveness — was just the kind of project that rich countries could justify to taxpayers. “It should be an easy case for South Africa, ourselves and others to make,” Dr. Bertozzi said.

He said the foundation was excited about the results, but tried to focus on riskier, longer-term research. The foundation has committed more than $250 million to microbicide research.

The hope is that two additional studies would provide the evidence to adopt the gel on a large scale. Three rigorous studies have established that male circumcision reduces a man’s risk of H.I.V. infection by at least half, and governments across Africa are beginning to offer it.

For the microbicide, researchers plan to lead one of the confirmatory studies in South Africa, where an estimated 5.7 million people are infected, more than in any other nation. Scientists would conduct the second study in five southern African nations.

Experts say investing in AIDS prevention is fiscally far preferable to the costs for lifelong treatment. Mead Over, a health economist at the Center for Global Development, says that providing antiretroviral therapy to the five million people with AIDS in Africa already receiving it will cost $72 billion over the next four decades. That amount rises to $225 billion if the number of people on treatment continues to grow.

“Donors should not be nickel and diming this research because by spending only $100 million they have a prospect of saving billions of dollars in treatment costs,” Mr. Over said.

Advocates make the case on humanitarian grounds.

“We see every day women getting infected by H.I.V.,” said Nomfundo Eland of the Treatment Action Campaign, an advocacy group here. “The sooner we can get a method in the control of women the better.”

Recurrent pneumonia increases lung cancer risk for patients with AIDS
Michael Carter
Published: 06 September 2010

Recurrent bacterial pneumonia is associated with an increased risk of lung cancer in patients with AIDS, US investigators report in the online edition of the Journal of Acquired Immune Deficiency Syndromes. The association between pneumonia and lung cancer was especially strong amongst patients below 50.

The investigators believe that recurrent pneumonia could be causing inflammation, which in turn increases the risk of lung cancer.

Amongst people with AIDS in the US, lung cancer is the third most common cancer. Cigarette smoking has been identified as the only factor significantly associated with lung cancer risk for people with HIV in a number of studies. However, a team of US investigators found that even after adjusting for cigarette smoking, lung cancer risk was still elevated amongst people with HIV.

People with HIV, especially if they have a weak immune system, are more likely to develop serious lung disease. Three types of pulmonary disease are classified as AIDS-defining: PCP pneumonia; tuberculosis (TB); and recurrent bacterial pneumonia.

Investigators hypothesised that individuals with AIDS who developed these diseases would be at increased risk of lung cancer, because of the inflammation that they cause in the lungs.

They therefore looked at the records of 322,675 individuals who were diagnosed with AIDS between 1977 and 2002 and linked these to cancer registries. They monitored the patients’ risk of lung cancer in the ten years after their diagnosis with AIDS.

Recurrent pneumonia represented 2% of all AIDS diagnoses, the figures for TB and PCP being 4% and 26% respectively.

There was no change in the incidence of bacterial pneumonia, but the incidence of TB fell after the introduction of effective HIV therapy in 1996.
In more than ten years of follow-up, there were 853 cases of lung cancer (83 cases per 100,000 person years).

Individuals with recurrent pneumonia had a significantly higher risk of lung cancer than patients without this disease (hazard ratio, 1.63; 95% CI = 1.08 to 2.46, p = 0.02).

Of note, patients with recurrent pneumonia had a significantly increased risk of lung cancer five to ten years after their first diagnosis (p = 0.04).

Recurrent pneumonia was associated with an increased risk of lung cancer for patients aged under 50 (HR = 1.99; 95% CI, 1.26 – 3.16; p = 0.003), but not for the over 50s.

The association between bacterial pneumonia and lung cancer risk did not vary significantly in the eras before and after effective HIV therapy was introduced.

Overall, lung cancer was not linked to TB. However, the investigators did note a significantly increased risk of lung cancer for TB patients in the first year after their diagnosis with this infection. They believe that this was probably because chest x-rays diagnosed disease which was already present, or because lung cancer activated latent TB.

The investigators did not have information about the patients’ smoking habits. However, on the basis of other research involving individuals with HIV, they assumed a smoking prevalence of at least 70% amongst the patients with recurrent pneumonia.

This weakened the association between recurrent pneumonia and lung cancer to the point where it ceased to be statistically significant (70% prevalence, HR = 1.42; 95% CI, 0.93–2.14).

Nevertheless, the investigators comment: “We found that individuals with recurrent pneumonia had a significantly increased risk of lung cancer...our current observation that recurrent pneumonia was associated with increased lung cancer risk among younger, but not older PWA supports the conclusion that pulmonary infections might explain the high lung cancer risk among young PWA.”

Reference
Shebl FM et al. Pulmonary infections and risk of lung cancer among persons with AIDS. J Acquir Immune Defic Syndr, advance online publication, August 23, 2010. (Link to abstract and full text publication)

High genital HIV levels may persist in women who appear to achieve viral suppression with use of ART
Kelly Safreed-Harmon
Published: 06 September 2010
HIV-positive women whose plasma HIV RNA viral loads drop to undetectable levels following initiation of ART still may have intermittent surges in the amount of virus in their genital secretions, according to a US study.

The study analysed changes over the course of one year in the plasma and genital tract HIV levels of US women taking ART. The journal AIDS has published the findings in an online article released in advance of print publication.

The findings have important HIV prevention implications in light of recent debates about the extent to which HIV-positive people with undetectable plasma viral load are still at risk of transmitting HIV to others.

In particular they highlight the need for evidence of viral load levels in genital secretions to be measured longitudinally in studies which monitor rates of HIV transmission in HIV-discordant sexual partnerships. Gathering these data would permit a better understanding of the clinical significance of episodic shedding of HIV in genital fluids when plasma viral load is suppressed.

Women who had plasma HIV viral load levels below 75 copies/mL at least six months before being screened for the study were eligible to participate. Fifty-nine women who met this requirement, all patients at an HIV clinic in the US state of Rhode Island, contributed a total of 582 study visits at which they underwent plasma and genital tract viral load testing.

More than half of all study participants had detectable genital tract viral load levels (>3300 copies/mL), a condition referred to as “HIV shedding,” at least once during the study period. Almost 40% of women had HIV shedding when HIV was undetectable in plasma.

Among women who had not undergone hysterectomies, the highest genital viral load levels observed in conjunction with undetectable plasma viral load were 456,000 copies/mL in the endocervix; 648,000 copies/mL in the ectocervix; and 480,000 copies/mL in the vagina.

The endocervix, ectocervix and vagina had about the same likelihood of yielding samples with detectable viral load during plasma viral load suppression.
Researchers tested vaginal samples from women who had undergone hysterectomies. In that group, the highest vaginal viral load level when HIV was undetectable in plasma was 68,000 copies/mL.

Researchers considered the potential role of STIs in increasing genital tract HIV shedding, but data on STIs in the study population did not suggest associations of that nature.

Overall, women without hysterectomies had HIV shedding in at least one of the three parts of the vaginal tract at 9% of study visits at which they also had undetectable plasma viral load levels (95% CI, 6% – 14%). Shedding was observed at 13% of all study visits (95% CI, 9% – 18%).

A component of the study looked at genital tract HIV levels over time in women who maintained undetectable plasma HIV viral load levels (less than 80 copies/mL) for at least three consecutive study visits.

Researchers assigned those women one of three classifications.

- “Persistent shedders” were those who had at least two consecutive study visits with undetectable plasma HIV levels but detectable genital tract HIV levels.
- “Intermittent shedders” had undetectable plasma HIV levels but detectable genital tract HIV levels at one visit in between two visits at which both genital tract and plasma HIV levels were undetectable.
- “Nonshedders” never had detectable HIV in the genital tract at the same time that their plasma viral load was below the level of detection.

Four of the 59 study participants (6.8%) were found to be persistent shedders; 18 (31%), intermittent shedders; and 27 (46%), nonshedders. The remaining 10 women did not meet the criterion of having three consecutive study visits with undetectable plasma viral load levels.

Researchers compared the combined group of persistent and intermittent shedders to nonshedders to try to identify sociodemographic and health-related factors that might help account for variations in genital viral load levels.

Women with hysterectomies, who constituted 19% of the study population, were less likely than other women to have genital HIV shedding (risk ratio 0.14, 95% confidence interval [CI], 0.02 – 0.99). No other differences were observed, but researchers noted that some other risk factors could not be ruled out on the basis of the statistical results.

In the full study cohort, having detectable plasma HIV viral load increased the odds of having detectable genital tract HIV viral load at the next visit. The inverse was not true – a detectable genital tract viral load level did not predict a subsequent detectable plasma viral load level.

Antiretroviral treatment failure was not an outcome for any study participant experiencing detectable genital tract HIV levels at the same time that plasma HIV levels were undetectable. The paper suggests that the “episodic, unpredictable nature of genital tract shedding” in study participants with undetectable plasma HIV viral load levels may make it difficult to assess the HIV transmission risk in such situations.

It concludes, “Whereas genital tract shedding is primarily driven by plasma viremia, clinicians may not be able to solely rely on [ART] to eradicate the potential for the sexual and perinatal transmission of HIV.”

Reference

CuBuvin S et al. Genital tract HIV-1 RNA shedding among women with below detectable plasma viral load. AIDS: advance online publication, August 31, 2010. DOI: 10.1097/QAD.0b013e32833e5043. (Link to abstract and full text article).

Untreated Individuals Show Increased HIV in Cells despite Stable Plasma Viral Load

SUMMARY: The amount of viral genetic material in peripheral blood immune cells rises steadily over time in HIV positive people who are not taking antiretroviral therapy (ART), according to Dutch study described in the July 17, 2010 issue of AIDS. HIV levels in these cells increased even if blood plasma viral load remained stable, and was associated with decreases in CD4 T-cell count.

By Liz Highleyman

People with HIV often have a long asymptomatic stage of infection before developing overt AIDS-related illnesses or severe immune deficiency indicated by low CD4 T-cell count. While HIV levels in the blood are typically stable in this phase—as production and elimination of virions (individual viral particles) is balanced—a growing body of evidence shows that the virus nevertheless causes damage during this period.

Alexander Pasternak from the Center for Infection and Immunity in Amsterdam and colleagues performed a study to compare the dynamics of HIV-1 molecular markers in peripheral blood mononuclear cells (PBMCs) and in blood plasma during the asymptomatic phase of infection in individuals not on ART.
Investigators used real-time PCR assays to measure levels of HIV proviral DNA (genetic material integrated into the host cell genome), unspliced HIV RNA, and multiply spliced RNA in PBMCs from 10 untreated men with subtype B HIV at multiple time points during asymptomatic infection. A total of 53 measurements were taken over an average of 4.6 years (range 1.5 to 10.6 years), paired with plasma viral load and CD4 cell readings.

**Results**

- Plasma HIV RNA levels did not significantly change in any of the study participants during the asymptomatic period.
- Levels of unspliced HIV RNA increased significantly over time, however, in PBMCs from 6 out of 10 people.
- Levels of proviral DNA increased in peripheral blood cells from 4 people.
- Amounts of unspliced RNA in PBMCs increased significantly faster over time than either plasma RNA or proviral DNA.
- Rising levels of unspliced RNA and proviral DNA in PBMCs were significantly associated with decreasing CD4 cell counts (P = 0.006 and 0.02, respectively).
- In contrast, there was no significant correlation between plasma HIV RNA viral load and CD4 cell loss.

Based on these results, the study authors concluded, "During the asymptomatic phase of untreated HIV-1 infection, when virion production and clearance are balanced, resulting in stable plasma viremia, viral load in PBMCs steadily increases and is a sensitive and direct longitudinal virological marker of infection progression."

To explain these findings, they suggested that "progressive weakening of the antiviral immune response during the asymptomatic phase might be one of the factors defining the temporal increase in the relative numbers of HIV-producing cells, and, therefore, the increase in HIV-1 replication rates in PBMCs..." Alternatively, "cellular and/or viral factors might influence the rate of viral replication in PBMCs."

Levels of HIV in PBMCs are a more direct and sensitive marker of disease progression during the asymptomatic phase of infection and may be more useful than standard plasma HIV RNA viral load testing, the researchers added.

**Reference**


**'Jailbreak' bacteria can trigger heart disease**

Plaque-causing bacteria can jailbreak from the mouth into the bloodstream and increase your risk of heart attack says a scientist at the Society for General Microbiology's autumn meeting in Nottingham. Professor Howard Jenkinson, from the University of Bristol explains how oral bacteria can wreak havoc if they are not kept in check by regular brushing and flossing. "Poor dental hygiene can lead to bleeding gums, providing bacteria with an escape route into the bloodstream, where they can initiate blood clots leading to heart disease," he said.

Streptococcus bacteria commonly live in the mouth, confined within communities termed biofilms and are responsible for causing tooth plaque and gum disease. The University of Bristol researchers, in collaboration with scientists at the Royal College of Surgeons in Ireland (RCSI), have shown that once let loose in the bloodstream, Streptococcus bacteria can use a protein on their surface, called PaDA, as a weapon to force platelets in the blood to bind together and form clots.

Inducing blood clots is a selfish trick used by bacteria, as Professor Jenkinson points out. "When the platelets clump together they completely encase the bacteria. This provides a protective cover not only from the immune system, but also from antibiotics that might be used to treat infection," he said.

"Unfortunately, as well as helping out the bacteria, platelet clumping can cause small blood clots, growths on the heart valves (endocarditis), or inflammation of blood vessels that can block the blood supply to the heart and brain."

Professor Jenkinson said the research highlights a very important public health message. "People need to be aware that as well keeping a check on their diet, blood pressure, cholesterol and fitness levels, they also need to maintain good dental hygiene to minimise their risk of heart problems."
The team is using a brand-new blood flow model, developed by Dr Steve Kerrigan at the RCSI, School of Pharmacy, Dublin, that mimics conditions in the human circulatory system. "We are currently investigating how the platelet-activating function of PadA can be blocked. This could eventually lead to new treatments for cardiovascular disease which is the biggest killer in the developed world," said Professor Jenkinson.

Talented bacteria make food poisoning unpredictable
While we are often exposed to bacteria in our food which could cause food poisoning, we don’t always become ill—why should this be so?

Professor Colin Hill who is presenting his work at the Society for General Microbiology’s autumn meeting in Nottingham today describes how bacteria use different tricks to aid their survival inside the body, helping to explain why food poisoning can be so unpredictable.

One of the biggest challenges faced by food-borne bacteria is acid. Acidic conditions, particularly in the stomach and in the gut will kill most microbes found in contaminated food.

Professor Hill’s group at University College Cork has revealed that Listeria bacteria, which may be found in soft cheeses and chilled ready-to-eat products, can overcome harsh acidic conditions by exploiting key food ingredients. Listeria that survive are able to cause serious and sometimes fatal infections, particularly in the elderly and pregnant women.

Certain food constituents such as the amino acid, glutamate, can help the bacteria neutralise acid, allowing the bacteria to pass through the stomach unscathed. Professor Hill explains the significance of this. "People who consume foods that are contaminated with Listeria and are also high in glutamate, such as soft cheese or meat products, have a higher chance of developing serious infection than someone eating the same quantity of bacteria in a low-glutamate food," he said. "Of course this is further complicated by the fact that a contaminated, low-glutamate food could be eaten in combination with a high-glutamate food such as tomato juice, which could also increase the risk of infection."

Listeria can also take advantage of food processing and storage conditions to help them survive. "Bacteria that are exposed to low pH before entering the body may adapt to become more acid-tolerant and therefore better equipped to deal with acidic conditions in the body. For example, Listeria contaminating naturally acidic foods such as cheese may be more likely to cause infection than Listeria carried at a more neutral pH in water."

Professor Hill explains how his group’s work could help reduce the incidence of Listeria infections. "The number of cases of listeriosis has nearly doubled in the last decade in Europe. This is because the bacterium is so good at overcoming the challenges it faces in food and in the body," he said. "Our studies show that consuming Listeria in one food may be quite safe, while eating the same amount in another food might be lethal. By understanding the role of the food matrix we may be able to identify and eliminate high-risk foods from the diet of susceptible people."

Next Step in Evolution? A Technical Life Form That Passes on Knowledge and Experience
ScienceDaily (Sep. 4, 2010) — Dutch biologist Gerard Jagers op Akkerhuis has developed the ‘operator hierarchy’—a system based on the complexity of particles and of organisms, which can predict the next step in evolution: a technical life form, that can pass on its knowledge and experience to the next generation.

Jagers will receive his doctorate from Radboud University Nijmegen on Monday 6 September.

Biologists' take on the hierarchy of life has been pretty careless up to now. This hinders the discipline, says Gerard Jagers op Akkerhuis. And there is room for improvement: following lengthy research Jagers came up with a hierarchy that is not only more consistent but also includes the classification of inorganic natural matter.

Following after the ‘memons’, the multicellulars with a neural network, Jagers predicts that the next closure will lead to a life form in which the transfer of the blueprint by means of genes is replaced with the transfer of knowledge and collective experience by so-called ‘memes’.

In Jagers’ view, memes are codes that determine the structure of the brain. In turn, the structure of the brain determines someone’s knowledge. In this way, memes are carriers of brain structure and the corresponding knowledge, just like genes are carriers of protein recipes and the corresponding cell physiology.
The next life form will not necessarily develop by means of biological evolution: as far as Jagers is concerned, a machine that shows intelligent behaviour based on a neural network fulfills the definition of life. If this system can then also pass on its memory to the next generation then this involves a new step in evolution. "However, for the time being such robots still need humans to build them."

McDonnell Seeks Money for Abstinence-Only Education

McDonnell Seeks Money for Abstinence-Only Education

Virginian-Pilot (Norfolk), (09.01.2010) Julian Walker

Gov. Bob McDonnell has decided to forgo a no-cost federal grant for comprehensive STD and pregnancy prevention among teens and instead apply for a $900,000 abstinence-only grant that requires a state match of $383,000.

McDonnell elected to apply for the abstinence grant partly because he has long supported funding for that type of education, said a spokesperson. Administration officials said the federal abstinence funds will not eliminate or interfere with sex education programs already being taught in public schools. Virginia uses the Family Life Education curriculum in at least 102 of its 132 school divisions.

The state chapters of Planned Parenthood and NARAL Pro-Choice had asked the governor to pursue the Personal Responsibility Education Program funds, which do not require state matching dollars. After McDonnell declined, Planned Parenthood Advocates of Virginia accused him of “fiscal malpractice.”

“Given Virginia’s economic situation, wasting $400,000 of taxpayer money for an ineffective program is not a good use of the commonwealth’s limited resources,” Jessica Honke, the group’s policy director, said in a statement.

“Despite the rhetoric from the economic loser in this decision, Planned Parenthood, recent studies have shown that abstinence education effectively helps teens postpone risky sexual behavior,” countered Victoria Cobb, president of the Family Foundation of Virginia.

State Sen. Ralph Northam (D-Norfolk), a physician, said that while abstinence is the goal, he is disappointed McDonnell passed on the opportunity to acquire federal funds with more flexibility of use. “There should be a comprehensive plan to sex education that strongly encourages abstinence-only, but it needs to be comprehensive,” he said.

Prejudice About Addiction Risks Thwarting New Policy

Prejudice About Addiction Risks Thwarting New Policy

The Guardian (London), (08.24.2010) Alan Travis

Stigma against drug users is a critical barrier to their treatment and social reintegration, according to the first installment of a four-part study by the independent UK Drugs Policy Commission (UKDPC).

Heroin and crack cocaine use, especially, can carry a “stigma life sentence,” the report said. For instance, two-thirds of employers said they would not hire a former heroin or crack user, even if he or she were suitable in all other respects, an earlier UKDPC survey found.

Some Tory reformers criticize methadone maintenance therapy, in which users are prescribed methadone for a prolonged, indeterminate period, as “parking” drug users. While evidence for methadone maintenance is strong, stigma against it as a “non-treatment” limits its expansion and optimal delivery, according to studies the UKDPC report cited.

An abstinence-based approach to addiction treatment, reportedly being considered by Britain’s new coalition government, could be undermined by stigmatizing attitudes, UKDPC warned.

The Department for Work and Pensions recently proposed docking the welfare benefits of drug users who do nothing about their addiction. The UK drugs minister, James Brokenshire, has acknowledged the importance of methadone programs in stabilizing problem drug users.

“Stabilizing users can then lead to a pathway of recovery where they are free of drugs and can contribute to society by gaining employment, not held in addiction,” Brokenshire said.

“The supervised consumption of methadone in pharmacies provides a unique context in which users’ status as problem drug users can be made public,” the report said. Many clients of pharmacy-based methadone and syringe exchange programs felt “outed” and reported distrust or prejudice by pharmacy staff and fellow customers. Drinking pink liquid from a small cup at the pharmacy is hard to hide, and yet segregating methadone clients from other customers can also be stigmatizing, the report noted.

A new test proved highly accurate at diagnosing TB and detecting resistance to rifampin, in less than two hours and with minimal hands-on time, a new study shows.

Traditional culturing can take a week or more. Using a microscope to look for TB bacteria is faster but can miss many cases and says nothing about resistance.

“If you have 50 patients in a clinic and one person looking at a microscope it could take hours and hours,” said Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases.

Among 1,730 patients with suspected drug-sensitive or multidrug-resistant TB, the automated molecular TB and rifampin-resistance test, Xpert MTB/RIF, correctly identified 98 percent of patients with smear-positive and culture-positive TB, more than 72 percent of smear-negative and culture-positive disease, and 98 percent of rifampin-resistant TB. The study found the test was 99.2 percent accurate in ruling out patients who did not have TB.

Such an assay could “revolutionize TB care,” according to Dr. Mario Raviglione, head of the World Health Organization’s Stop TB Department. WHO will meet with experts over the next few days to review the data and make plans for next steps, he said.

Further evaluation will see whether the Xpert MTB/RIF test can detect multidrug-resistant TB. TB that is resistant to rifampin is often resistant to another commonly used treatment, said Fauci.

With relatively minimal training, a health care worker using the test could diagnose TB and rifampin resistance within 90 minutes, according to Dr. Catharina C. Boehme, of the Switzerland-based Foundation for Innovative New Diagnostics (FIND), and colleagues. It takes only 15 minutes of manual labor to take the mucous sample, mix it with chemicals and place it into an inkjet-like cartridge that goes into the $30,000 machine. The test costs about $63 in Europe, where it went to market last year. Cepheid, the test maker, pledges to offer the test to developing countries for less than half that price and to discount the machine to $20,000.

The Bill & Melinda Gates Foundation supported the study, along with the US National Institutes of Health, while FIND designed, supervised, and funded it.


Noting that efforts to improve early detection and access to HIV services “have increased over time,” the authors assessed patients’ immune status at initial presentation for HIV care in 13 US and Canadian clinical cohorts from 1997 to 2007.

The data analyzed concerned 44,491 HIV-positive patients enrolled in the North American-AIDS Cohort Collaboration on Research and Design. Initial presentation for HIV care was identified as the time of the first CD4+ T lymphocyte (CD4) count. Patients who had HIV RNA measurements, evidence of exposure to antiretrovirals or a history of AIDS-defining illness prior to the first CD4 count were excluded from the analysis. Linear regression adjusted for age, sex, race/ethnicity, HIV transmission risk, and cohort was used to determine trends in mean CD4 count (measured as cells/mm3) and 95 percent confidence intervals (CI).

Over time, median age at initial presentation for HIV care increased (range 40-43 years; P<.01), while the proportion of patients at risk of HIV through injection drug use decreased (from 26 percent to 14 percent; P<.01) and heterosexual transmission risk increased (from 16 percent to 23 percent; P<.01). During the study period, median CD4 count at presentation increased from 256 cells/mm3 (interquartile range, 96-455 cells/mm3) to 317 cells/mm3 (interquartile range, 135-517 cells/mm3). The proportion of patients with a CD4 count of 350 or greater at first presentation rose from 38 percent to 46 percent (P<.01). The estimated adjusted mean CD4 count increased at a rate of 6 cells/mm3 per year (95 percent CI, 5-7 cells/mm3 per year).

“CD4 count at first presentation for HIV care has increased annually over the past 11 years but has remained <350 cells/mm3, which suggests the urgent need for earlier HIV diagnosis and treatment,” the authors concluded.
Bisexual Concurrency, Bisexual Partnerships, and HIV Among Southern African Men Who Have Sex with Men

*Sexually Transmitted Infections* Vol. 86: P. 323-327; (08..2010) Chris Beyrer; Gift Trapence; Felistus Motimedi; Eric Umar; Scholastika Iipinge; Friedel Dausab; Stefan Baral

Noting that the “sexual behavior of men who have sex with men (MSM) in southern Africa has been little studied,” the authors presented the first data on bisexual partnerships and bisexual concurrency among MSM in Botswana, Malawi, and Namibia.

A structured survey instrument and rapid-kit HIV screening were used to obtain a cross-sectional probe of a convenience sample of 537 men who had ever reported anal sex with another man.

Of the MSM, 34.1 percent were married or had a stable female partner, and 53.7 percent reported both male and female sex partners in the previous six months. Bisexual concurrency was common, with 16.6 percent of MSM reporting concurrent relationships with both a man and a woman. Bivariate analyses showed any bisexual partnerships were associated with lower education (odds ratio [OR] 1.6, 95 percent confidence interval [CI] 1.1 to 2.3); higher condom use (OR 6.6, 95 percent CI 3.2 to 13.9); less likelihood of having ever tested for HIV (OR 1.6, 95 percent CI 1.1 to 2.3); less likelihood of having disclosed sexual orientation to family (OR 0.47, 95 percent CI 0.32 to 0.67); and being more likely to have received money for casual sex (OR 1.9, 95 percent CI 1.3 to 2.7). Bisexual concurrency was associated with higher self-reported condom use (OR 1.7, 95 percent CI 1.0 to 3.1); being employed (OR 1.8, 95 percent CI 1.2 to 2.9); lower likelihood of disclosure of sexual orientation to family (OR 0.37, 95 percent CI 0.22 to 0.65); and having paid for sex with men (OR 2.0, 95 percent CI 1.2 to 3.2).

“The majority of MSM in this study report some bisexual partnerships in the previous six months. Concurrency with sexual partners of both genders is common. Encouragingly, men reporting any concurrent bisexual activity were more likely to report condom use with sexual partners, and these men were not more likely to have HIV infection than men reporting only male partners,” the authors concluded. “HIV prevention programs focusing on decreasing concurrent sexual partners in the African context should also target bisexual concurrency among MSM. Decriminalization of same-sex practices will potentiate evidence-based HIV prevention programs targeting MSM.”

Novel sensing mechanism discovered in dendritic cells to increase immune response to HIV

New York, NY (September 8, 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."

**Is Hand Washing Enough to Stop the Spread of Disease?**

ScienceDaily (Sep. 7, 2010) — Not drying your hands thoroughly after washing them, could increase the spread of bacteria and rubbing your hands whilst using a conventional electric hand dryer could be a contributing factor. Frequently people give up drying their hands and wipe them on their clothes instead, but hand-hygiene is a key part of infection control and drying hands after washing is a very important part of the process.

A study by researchers at the University of Bradford and published in the *Journal of Applied Microbiology* looked at different methods of hand drying, and their effect on transfer of bacteria from the hands to other surfaces. The different methods included paper towels, traditional hand dryers, which rely on evaporation, and a new model of hand dryer, which rapidly strips water off the hands using high velocity air jets.

Our bodies naturally have bacteria called commensals all over them. However, bacteria from other sources, such as raw meat, can also survive on hands, and can be easily transferred to other surfaces, increasing the risk of cross-contamination. When hands are washed the number of bacteria on the surface of the skin decreases, but they are not necessarily eliminated. If the hands are still damp then these bacteria are more readily transferred to other surfaces.

In this study the researchers quantified the effects of hand drying by measuring the number of bacteria on different parts of the hands before and after different drying methods. Volunteers were asked to wash their hands and place them onto contact plates which were then incubated to measure bacterial growth. The volunteers were then asked to dry their hands using either hand towels or one of three hand dryers, with or without rubbing their hands together, and levels of bacteria were re-measured.

Dr Snelling and her team found that rubbing the hands together whilst using traditional hand dryers could counteract the reduction in bacterial numbers following handwashing. Furthermore, they found that the relative reduction in the number of bacteria was the same, regardless of the hand dryer used, when hands are kept still. When hands are rubbed together during drying, bacteria that live within the skin can be brought to the surface and transferred to other surfaces, along with surface bacteria that were
not removed by handwashing. The researchers found the most effective way of keeping bacterial counts low, when drying hands, was using paper towels. Amongst the electric dryers, the model that rapidly stripped the moisture off the hands was best for reducing transfer of bacteria to other surfaces.

Dr Snelling says: "Good hand hygiene should include drying hands thoroughly and not just washing. The most hygienic method of drying hands is using paper towels or using a hand dryer which doesn’t require rubbing your hands together."

**Journal Reference:**


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**Imaging Reveals Key Metabolic Factors of Cannibalistic Bacteria**

ScienceDaily (Sep. 7, 2010) — Researchers at the University of California, San Diego have revealed new details about how cannibalistic bacteria identify peers suitable for consumption. The work, which employed imaging mass spectrometry, is a first step toward a broader effort to map all signaling molecules between organisms.

"These are the molecules that control biology," said Pieter C. Dorrestein, PhD, associate professor at UC San Diego's Skaggs School of Pharmacy and Pharmaceutical Sciences and corresponding author of a paper published in the online edition of the *Proceedings of the National Academy of Sciences*.

Bacterial cannibalism occurs when a subpopulation of a microbial colony eats another subpopulation, harvesting the latter's nutrients to sustain growth in times when external food sources are limited. The phenomenon is well-known, but not well-characterized. For example, researchers have not known exactly how microbes identify, select and kill their genetically identical siblings.

Dorrestein, with colleagues at UC San Diego and in Iowa and Texas, studied *Bacillus subtilis*, a common species with a complex life cycle that thrives in diverse living conditions, from soil to contaminated wounds to the intestinal tract. Using imaging mass spectrometry, the researchers generated spatial distributions or chemical maps of molecules within the microbe, focusing in particular on two metabolites called sporulation delaying protein (SDP) and sporulation killing factor (SKF), which the scientists correctly hypothesized were directly involved in the cannibalistic process.

"These are the first fully characterized molecules that enable *B. subtilis* to 'digest' or differentiate genetically identical cells," said Dorrestein. "Our work also shows that the molecules the bacteria uses to differentiate themselves are akin to those of a multicellular organism, even though the microbes are genetically identical. Most people do not think of a microbial colony as a differentially organized multicellular organism."

Since SDP and SKF were involved in killing bacteria, the scientists also explored whether the molecules might be effective weapons against human pathogens. Their findings were mixed. SKF had no effect on targeted pathogens like *Pseudomonas aeruginosa* or *Klebsiella pneumonia*, but SDP displayed potent inhibitory activity against two variants of *Staphylococcus aureus* and other pathogens. Dorrestein said SDP itself has limited potential as an antibacterial agent, "but it could serve as an antibiotic lead compound where the active portion can be modified to meet the requirements of a therapeutic agent. It further shows that imaging mass spectrometry can be used to discover biologically active molecules."

He said additional antibacterial molecules are likely to be found in other cannibalistic species, but they remain to be identified and described.

**Journal Reference:**


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**Majority of People with Late-stage HIV Disease Still Have Virus that Uses CCR5 Co-receptor**

**SUMMARY:** Nearly two-thirds of HIV positive people with late stage disease still carry only virus strains that use the CCR5 co-receptor to enter CD4 cells, according to a report in the *August 24, 2010 issue of AIDS*. Past research has linked advanced disease with virus that uses the CXCR4 co-receptor, but this study found that CCR5 use is more common at this stage and patients with only CCR5-tropic virus were more likely to develop AIDS-defining illnesses. These findings indicate that many people with advanced disease could potentially benefit from using the CCR5 antagonist *maraviroc (Selzentry)*.

**By Liz Highleyman**
HIV-1 can use 2 different co-receptors—CCR5 and CXCR4—along with the CD4 surface receptor to enter cells. An individual may carry HIV that only uses CCR5, only uses CXCR4, or can use either gateway (dual tropism), or they may have a combination of CCR5-tropic and CXCR4-tropic strains (mixed tropism). CCR5-tropic HIV is more likely to be found in people with advanced disease, and some studies have shown that CXCR4-tropic strains are more aggressive, but this link is not fully understood.

Benedikt Simon from the Medical University of Vienna and colleagues sought to determine the relative proportions of HIV strains with different co-receptor tropism in treatment-naive individuals with late-stage disease, and to examine the relationship between tropism and markers of HIV disease progression including viral load, CD4 cell count, and clinical symptoms.

The study included 50 participants who were first diagnosed with HIV after they had already sustained serious immune system damage. All had CD4 counts < 200 cells/mm3 and none had previously taken antiretroviral therapy (ART). Such late presenters have an elevated risk of death and their treatment may be more complicated than it is for people diagnosed earlier, the study authors noted as background.

**Results**

- Co-receptor tropism testing showed that 62% of participants carried only CCR5-tropic HIV strains.
- People with a history of injection drug use were significantly more likely to have CXCR4-tropic or dual/mixed-tropic HIV than those presumed infected through sex (P = 0.02).
- Co-receptor tropism was not associated with significant differences in CD4 cell count or viral load at the time of diagnosis.
- Baseline CD4 count was slightly higher among individuals with only CCR5-tropic HIV (61 vs 32 cells/mm3, respectively), but the difference did not reach statistical significance.
- Only in very late presenters—those with CD4 counts < 50 cells/mm3—did the researchers see significant differences in disease stage at the time of presentation.
- Within this subgroup, people with only CCR5-tropic HIV were actually more likely to have CDC stage 3 disease—or AIDS-defining conditions—than individuals carrying CXCR4-tropic or dual/mixed-tropic strains (P = 0.04).
- About 90% of very late stage patients with only CCR5-tropic HIV developed AIDS-defining illnesses compared with about 50% of those with CXCR4-tropic or dual/mixed strains.

Based on these findings, the researchers concluded, "A substantial number of patients diagnosed at a late stage of HIV-1 infection may be infected exclusively with [CCR5]-tropic virus strains, making this specific patient group a possible candidate for coreceptor antagonist treatment."

Maraviroc is currently the sole FDA-approved CCR5 antagonist. People considering the drug receive a co-receptor tropism test such as the Trofile assay to ensure that they only carry CCR5-tropic virus. Maraviroc may be particularly beneficial for patients with late-stage disease, since some studies have shown that raises CD4 counts more than other antiretroviral drugs.

**Blood Donor Ban Upheld**

*Toronto Star*, (09.10.2010)

In a 187-page decision released Thursday, Justice Catherine Aitken of the Superior Court of Justice upheld the Canadian Blood Services’ (CBS) ban on donations by men who have sex with men (MSM).

Giving blood is not a civil right on par with voting, marrying or holding public office, Aitken said.

In Canada, any man who has had sex with a male partner since 1977 is ineligible for blood donation. Aitken pointed to epidemiological evidence showing that HIV and other STDs are more prevalent in the blood of MSM than heterosexuals. Though concerns about the validity of the scientific research have been raised, CBS has a right to err on the side of caution, the judge said.

“It would be irresponsible of [CBS] as a blood operator to wait until there is clear scientific evidence regarding a risk before taking reasonable steps to avoid it,” Aitken said.

Aitken acknowledged that many MSM may feel a sense of injustice over being denied the opportunity to donate blood, a reaction that could be “all the stronger and more poignant” given the history of
discrimination against the MSM community. “That impact, however, is not in the same league as the impact on a blood recipient who has to use blood or blood products in order to survive or make life livable and who is asked to accept lower safety standards,” she wrote.

Aitken awarded $10,000 (US $9,648) in damages to CBS after finding that a gay man, Kyle Freeman, committed negligent misrepresentation when he donated blood as many as 18 times between 1990 and 2002, falsely denying he had ever had sex with another man. In 2002, his donation was discarded after it tested positive for syphilis. In an anonymous e-mail to CBS, which the blood service obtained a court order to trace, Freeman admitted his deception and voiced his objections to the ban. Aitken dismissed Freeman’s counterclaim of equality rights against CBS and the federal attorney general.

Namibian Women with HIV Tell Court of Forced Sterilizations

_Agence France Presse_, (09.09.2010)

Friday is expected to be the final day of testimony in the case of three Namibian women who say they were forcefully sterilized while in labor because they are HIV-positive. Sixteen women are suing the Namibian government for $1.2 million (US $165,000) each for allegedly sterilizing them without their consent.

In August 2008, legal aid groups and a women’s AIDS organization presented to the Health Ministry the cases of more than 40 women who have suffered a similar experience. The current case is the first of its kind in Africa.

The incidents occurred at three state hospitals—one in the capital, Windhoek, and one about 440 miles north in Oshakati, the women claim. In court testimony last week, one of the women said she was given a document to sign, during labor, that would authorize a cesarean section. “I did not know this was also for sterilization,” she told the court, speaking through an interpreter. She discovered she had been sterilized only after she overheard two nurses saying the surgery was conducted because she has HIV.

According to the government, an investigation at state hospitals around the country found that all the women had signed consent forms for the sterilization procedure. “The investigation clearly established that all women who had had a cesarean section as well as a sterilization had signed the relevant consent forms before the operation was done,” Health Minister Richard Kamwi told Parliament ahead of the trial.

Forms signed while a woman was already in labor should not be considered valid, gynecologist Matti Kimberg told the court. Priti Patel, AIDS program manager at the Southern Africa Litigation Center, noted, “The women were not aware of their right to say ‘no’ to sterilization.”

Prevalence and Correlates of Trichomonas Vaginalis Infection Among Female US Federal Prison Inmates

_Sexually Transmitted Diseases Vol. 37; No. 9; P. 585-590_, (09..2010)  Siobhan Sutcliffe; Sara B. Newman; Andrew Hardick; Charlotte A. Gaydos

Previous studies have noted Trichomonas vaginalis prevalence rates of 22 percent to 47 percent among women entering US jails and state prisons. The authors of the current report sought to determine prevalence of the STD among inmates in two female-only federal prisons in the United States.

At the two facilities, 624 women were recruited and completed a self-administered questionnaire. Self-collected specimens, first-catch urine sample and vaginal swab, were tested for T. vaginalis DNA.

A positive urine result or vaginal swab result or both were noted for 8.5 percent of participants at one prison and 8.3 percent of participants at the other; combined prevalence was 8.5 percent. With positivity in either specimen as the reference standard, urine polymerase chain reaction had a sensitivity of 66.7 percent; vaginal swab PCR had a sensitivity of 84.4 percent.

Lower household income before arrest was found to be the only significant positive correlate of T. vaginalis infection. Other factors with nonsignificant positive correlation to T. vaginalis infection were being employed at the time of arrest; having experienced sexual, physical or emotional abuse by a family member; having a parent who had not had a drug or alcohol addiction; never exchanging sex for money or drugs; ever being pregnant; having abnormal vaginal bleeding/spotting; and having concurrent chlamydia or gonorrhea.

“Although not as high as in other studies of women entering US jails and state prisons, our observed T. vaginalis prevalence of 8.5 percent was much higher than in the general US population,” the authors concluded. “Therefore, screening for T. vaginalis infection may be warranted at federal prison entry, as well as sexual health education during prison stay.”
IPS Examines Obstetric Fistula In Africa
Inter Press Service examines how women’s "low status" can contribute to the development of obstetric fistulas in women in "East, Central and Southern Africa."

"Very young women or girls face a higher risk of fistula because their bodies have not fully developed; the continuing practice of early marriage in many parts of the continent, and the frequent absence of family planning place women at risk. ... Women's low status means the decision to spend precious money on fees for medical care – or even transport to the nearest facility – is deferred as long as possible. Many women across Africa give birth at home, and the absence of a skilled attendant increases the risk that the danger signs of obstructed labour will be missed, and there will be no one to take appropriate emergency measures," the news service writes.

To address some of the causes of obstetric fistula, the East, Central and Southern African Health Community (ECSA-HC) – an organization that aims to encourage health cooperation – has created a regional policy document, which will be presented to health ministers ahead of a summit in Zimbabwe in October. It provides recommendations on how governments can improve health care so the condition can be prevented.

The article includes quotes from a reproductive health specialist, a member of the ECSA-HC staff and a physician who works for the Mauritian health ministry (Anyangu-Amu, 9/10).

How mycobacteria avoid destruction inside human cells
Newly published in PLoS Pathogens
Tuberculosis, or TB, is a dreaded contagious disease of the lungs and other organs. The causative agent, *Mycobacterium tuberculosis* (or *M. tuberculosis*), infects roughly a third of the world’s population and one-in-ten to one-in-twenty of the infected population becomes sick or infectious at some point during their lifetime.

The mycobacteria survive, and even thrive, inside host macrophages – cells that are part of the human immune system and that usually engulf and destroy bacteria in structures called phagosomes. *M. tuberculosis* is taken into phagosomes but it somehow blocks phagosome maturation, and hence survives. Figuring out how could open up new therapeutic targets for the treatment of TB as well as shedding light on the mechanism of intracellular parasitism.

Researchers at the Pasteur Institutes in Seoul and Paris and Institute of Pharmacology and Structural Biology (IPBS) in Toulouse joined forces to systematically search for mycobacterial genes that block phagosome maturation. To do this, they generated 11,000 different mutants of the *M. tuberculosis* Beijing strain, which has been associated with large outbreaks of TB, increased virulence, and multidrug resistance.

Using a high-throughput visual assay, the researchers screened for mutant mycobacteria that had lost the ability to arrest phagosomal maturation. Lead author Dr. Priscille Brodin, heading the Inserm Avenir Unit at Institut Pasteur Korea describes the screen as "enabling stringent selection of mutants that have the most pronounced subcellular localization within intracellular acidic compartments through the use of automated confocal quantitative imaging. Our approach", she adds, "may be useful to identify virulence genes in other intracellular pathogens".

The team identified ten distinct mutants, only one of which had previously been shown to play a part in phagosome maturation arrest. Finding that two independent mutants mapped to the same region, they studied this locus in more detail. The work revealed that the biosynthesis of particular glycolipids containing acyltrehalose was perturbed, suggesting to the researchers that these glycolipids play a critical role in the early intracellular protection of mycobacteria.

"Our study unravels the role of novel lipid molecules in mycobacterial intracellular parasitism" says Dr. Olivier Neyrolles leading a CNRS Unit at IPBS in Toulouse France. "This establishes potential new drug targets", especially important given the emergence of multidrug-resistant and extensively drug-resistant TB. "In addition", Dr Brodin points out, "the assay that have we developed can be readily adapted for the screening of novel antimicrobials".

Pope’s anti-condom message is sabotage in fight against Aids
Stance makes Catholic church a major global public health problem
Condoms do not immunise against infection but they are an effective barrier against the HIV virus.
This week the pope is in London. You will have your own views on the discrimination against women, the homophobia, and the international criminal conspiracy to cover up for mass child rape. My special interest is his role in the 2 million people who die of AIDS each year.

In May 2005, shortly after taking office, the pope made his first pronouncement on AIDS, and came out against condoms. He was addressing bishops from South Africa, where somebody dies of AIDS every two minutes; Botswana, where 23.9% of adults between 15 and 49 are HIV positive; Swaziland, where 26.1% of adults have HIV; Namibia (a trifling 15%); and Lesotho, 23%.

Pope Benedict XVI explained that AIDS is a tragedy "that cannot be overcome through the distribution of condoms, which even aggravates the problems". In May 2009, the Congolese bishops conference made a happy announcement: "In all truth, the pope's message which we received with joy has confirmed us in our fight against HIV/AIDS. We say no to condoms!"

His stance has been supported, in the past year alone, by Cardinal George Pell of Sydney and Cardinal Cormac Murphy O'Connor, the Archbishop of Westminster. "It is quite ridiculous to go on about AIDS in Africa and condoms, and the Catholic Church," says O'Connor.

"I talk to priests who say, 'My diocese is flooded with condoms and there is more AIDS because of them.'"

Some have been more imaginative in their quest to spread the message against condoms. In 2007, Archbishop Francisco Chimoio of Mozambique announced that European condom manufacturers are deliberately infecting condoms with HIV to spread AIDS in Africa. Out of every 8 people in Mozambique, one has HIV.

It was Cardinal Alfonso López Trujillo of Colombia who most famously claimed that the HIV virus can pass through tiny holes in the rubber of condoms. Again, he was not alone. "The condom is a cork," said Bishop Demetrio Fernandez of Spain, "and not always effective."

In 2005 Bishop Elio Sgreccia, president of the Pontifical Academy for Life, explained that scientific research has never proven that condoms "immunise against infection".

He's right, they don't. They stop the virus which kills you from being transmitted during sex.

How effective are they? It's wise not to overstate your case. The current systematic review of the literature on this question published by Cochrane found 14 observational studies (because it's unethical to do a randomised trial where you actively stop people using condoms, since you know that they work but just want to find out how well).

These studies generally looked at HIV transmission in stable couples where one partner had HIV. Many of them looked at transfusion patients and haemophiliacs. Overall, rates of HIV infection were 80% lower in the partners who reported always using a condom, compared to those who said they never did. 80% is pretty good.

There is no single perfect solution to the problem of AIDS: if things were that easy, it wouldn't be killing 2 million people every year.

ABC is a widely used prevention acronym in Africa: abstain, be [faithful], [use a] condom. Picking out one effective measure and actively campaigning against it is plainly destructive, just as telling people to abstain doesn't make everyone abstain, and telling people to use condoms won't make everyone use them. But Ratzinger has proclaimed: "The most effective presence on the front in the battle against HIV/AIDS is the Catholic church and her institutions."

This is ludicrous. You, the Catholic church, is the only major influential international political organisation that actively tells people not to do something that works – on a huge scale. Your own figures show that your numbers are growing in Africa, even faster than the population does.

I'm happy for you to suggest abstinence. But sabotaging an effective intervention which prevents a disease that kills 2 million people a year makes you a serious global public health problem.

US Church Wants to Resume Zimbabwe AIDS Work


Police in Harare have detained six workers at an AIDS orphanage supported by a California church, claiming they were operating an unlicensed clinic and dispensing medicine without a pharmacist’s supervision. The six, five Americans and one Zimbabwean, are due in court Monday, according to their lawyer in Zimbabwe.

The Allen Temple Baptist Church in Oakland, Calif., began its ministry in Zimbabwe in 2000. Minister Theophous Reagans said one of the Americans lives in Zimbabwe, while the others visit three or
four times a year, paying their own way to help at the orphanage. “Our prayers and our hope is that they
will be released,” said Reagans.

Robert C. Scott, an Allen Temple member, AIDS activist and doctor who died last year, started the
church’s work in Zimbabwe after he and other members attended an international AIDS conference in
South Africa. On a trip to neighboring Zimbabwe, they were moved by what they saw at the Mother of
Peace Orphanage just outside Harare.

“Dr. Scott worked diligently for 10 years to build that ministry and serve. We want to continue,” said
Reagans, noting that most of Allen Temple’s members are black and feel a strong connection to Africa.

Robert Mugabe, Zimbabwe’s long-time ruler, is suspicious of independent aid groups, believing they
support his opposition, and he makes it difficult for them to access donor funds. Conditions for aid
workers have eased somewhat since Mugabe was forced into a power-sharing agreement with Morgan
Tsvangirai as prime minister last year.

Reagans said his church had not been affected by some of the problems encountered by other aid
groups. “We really believe that for the last nine, 10 years, we have been working in consort with the
authorities in Zimbabwe,” he said.

Older and Swinging: Need to Identify Hidden and Emerging Risk Groups at STI
Clinics

Patients who are swingers—heterosexual couples who participate in mate swapping and group sex, and visit sex clubs for
couples—comprise a “substantial portion” of sexually transmitted infection consultations, according to the
current study. While the authors noted that identifying STI risk groups “is essential for optimal
prevention and medical care,” they observed that swingers have not been considered a specific risk group
for STIs in health care services and prevention. The purpose of the team’s research was to compare STI
prevalence rates in swingers with those of other risk groups.

Since 2007, the registration system at the STI clinic in South Limburg has noted whether an attendee
is a swinger. The researchers analyzed STI clinic surveillance data to assess the swinger population’s share
of consultations and diagnoses for Chlamydia trachomatis (CT) and Neisseria gonorrhoea (NG).

Of 8,971 consultations, 12 percent comprised swingers (median age 43 years, IQR 38-48). The highest
STI prevalence was found in youths, men who have sex with men, and swingers. Among older swingers,
CT prevalence was 10 percent, and NG prevalence was 4 percent. The share of STI diagnoses among those
older than 45 comprised 55 percent for swingers and 31 percent for MSM.

Swingers “are a mainly older age group and form an important part of STI diagnoses,” the authors
concluded. “While other risk groups for STI, such as young heterosexuals and MSM, are systematically
identified at STI health care facilities and provided with appropriate services, this is generally not the case
for swingers. Swingers, like other groups with risk behaviors, need to be identified and treated as a risk
group in STI prevention and care.”

FDA: Abbott Recalls Some HIV Blood Screening Tests

The Food and Drug Administration said Thursday that Abbott Laboratories has recalled some HIV blood
tests after customers complained of “calibration failures.” Approved by FDA almost a year ago, the Prism
HIV O Plus test is used by laboratory professionals. Abbott says it is the first fully automated blood
screening test for HIV-1 and HIV-2. Abbott spokesperson Don Braakman said the company knows of no
effect on blood donations or the supply of blood products. The company notified its customers and FDA of
the problem last week and already has replaced the lot in question, he added. The recalled tests carry lot
number 87334M500. FDA said customers who have an alternate supply of the product should stop using
the recalled lot and discard it. Customers with no alternate supply should continue using the recalled lot
until replacement tests arrive. For more information, visit

Trial of Sterilized HIV-Positive Namibians Delayed

After 10 days of hearings, a judge announced on Friday a four-month delay in the case of three HIV-
positive women who claim they were involuntarily sterilized during labor at government hospitals. More
than 40 women took their allegations about the practice to the health ministry in August 2008; complaints filed by 13 of them will be handled after the current proceedings end. All 16 plaintiffs are suing for $1.2 million each (US $165,000). Observers had expected the trial to conclude Friday; Judge Elton Hoff now says hearings will continue on Jan. 18.

**Experts Warn Dip In Antibiotic R&D Could Lead To Treatment Challenges**

The 50th annual meeting of the *Interscience Conference on Antimicrobial Agents and Chemotherapy* (ICAAC) kicked off in Boston on Sunday with experts warning that a "slowdown" in research on antibiotic development could result in treatment challenges, *Agence France-Presse* reports.

"We have a big resistance problem that has become a global health crisis," Ursula Theuretzbacher of the Austrian Center for Anti-Infective Agents said at the conference. AFP added that "Theuretzbacher said thousands of people were being affected and dying from multidrug resistance, which had become a big problem in developing—as well as in—developed countries."

The article notes the reduction in scientific research on antibiotic development by 50 percent over the past 10 years, as described by Johnson and Johnson's Gary Noel, who gave several reasons for the decline. It also includes additional comments by Theuretzbacher, who proposes the creation of public-private partnerships to fill the gaps in antibiotic development funding and calls for greater regulation of antibiotics (Santini, 9/13).

"Drug resistance in bacteria, blamed on excessive and improper use of antibiotics, is not new, and health experts warn of an increasingly dangerous environment where the problem can flourish," *AFP* writes in a separate article. The article points to the *Lancet* study published last month, which identified a gene enabling bacteria to resist most antibiotics as a sign of the growing threat of antibiotic resistance. The article includes comments by Lindsay Grayson of Austin Hospital in Melbourne, Australia, who is program chair of the ICAAC conference, who was quoted as saying on the topic of antibiotic resistance, "There is still time and plenty of opportunities to fix things."

The ICAAC meeting will run through Tuesday, September 14, with an estimated 12,000 in attendance, according to the news service (Santini, 9/11).

**TIME Examines How Funding Cuts To Romania By International Donors Could Reverse The Country's Gains In HIV Fight**

*TIME* reports on how the recent withdrawal of funds for Romania’s HIV programs by international donors could threaten the country's efforts to prevent the spread of the virus. "According to UNAIDS, since 2001, HIV prevalence in the [Eastern Europe and Central Asia] region has risen by 66% to include 1.5 million people. ... The problem, experts say, is lack of funding for HIV prevention and of political will to work with stigmatized groups." The article examines how in Romania, NGOs have worked for a decade to offer HIV prevention programs, such as needle-exchange programs, to vulnerable populations in the country, and the impacts such efforts have had on HIV rates among injecting drug users (IDUs), which stand at "just 1%—the lowest in Eastern Europe."

However, "nearly four years after Romania joined the European Union, the World Bank no longer classifies Romania as a developing country, making it ineligible for a number of international grants" – the major funding source for the HIV prevention programs operated by the NGOs in Romania. "Since June, UNICEF, the Open Society Institute and the Global Fund to Fight AIDS, Tuberculosis and Malaria have all withdrawn funding for the country's HIV programs."

Experts warn that without funding for HIV prevention "Romania's HIV problem could get very serious, very fast," the magazine writes. "That has consequences for the rest of Europe too. Freedom of movement within the E.U. makes it easier for disease to spread; what's more, in 2008 Romania surpassed Russia to become the largest supplier of migrant sex workers to the E.U."

The article includes comments by NGOs and other HIV advocates on the ground as well as the country coordinator for UNAIDS (Adams, 9/20).

**Concerns Of Dengue Spread Ahead Of Commonwealth Games In New Delhi**

The Indian health ministry has confirmed 1,438 cases of dengue in New Delhi, but doctors say the estimate "likely was too low," *Bloomberg* reports (Srivastava, 9/12). "Dr. Chusak Prasttisur, the Southeast Asia coordinator of communicable disease for the World Health Organization, expressed concerns that the worst of the epidemic was to come. ...But K. Sujatha Rao, the health secretary, said Friday that the number of cases in New Delhi this year was no higher than usual," the *New York Times* reports, adding...
that the country is scrambling "to finish construction projects in time for the Commonwealth Games, which will take place here in less than a month. ... the athletes' quarters will be near a breeding ground for the mosquitoes that spread the disease" (Kumar, 9/10). Rao "said government workers have done all that they could to kill the adult Aedes mosquitoes that transmit dengue and their larvae at all the places in the city that they could access," and are fogging and spreading pesticides to kill the mosquitoes, according to the Wall Street Journal (Pokharel, 9/11).

Zimbabwe: 'Jealous Harare Aids Charity' Blamed for American Arrests
Irene Madongo
13 September 2010
The lawyer representing four Americans arrested on charges of distributing HIV drugs without licenses says a jealous Zimbabwe Aids charity is to blame for the saga.

Four American citizens, who are part of a Christian volunteer health service of the Allen Temple AIDS Ministry based in California, were arrested last Thursday in Harare, allegedly for disbursing antiretroviral drugs without a license. On Monday they were each charged $200 bail and released. It is anticipated that their case will be heard later in September.

The group includes one doctor, two nurses and a community volunteer. Two Zimbabwean doctors working with them were also arrested on related charges. The group operated from two clinics, one in Mutoko and another in Harare, where they worked primarily with AIDS orphans and HIV positive people. But the sudden arrests aroused suspicion as the organisation has operated in the country for the past decade.

Lawyer Jonathan Samukange said: 'They were working at a place called the Centre for Aids. There was a misunderstanding there so they moved. We suspect that the people from the old place they used to operate from are the ones who went to the police to make a report to say these people are operating without proper documentation. We suspect the whole thing was not police initiated, but initiated by a jealous previous partner.'

The Centre is a Harare-based charity that provides counselling and information to people with HIV/AIDS. When asked to comment on the allegations, the Centre's Executive Director Freddy Kachote vehemently denied his organisation had any involvement in the arrests.

When asked why the workers legal representative would single them out of all the organisations, Kachote replied: "Why would we speak to police? We have had a longstanding relationship with the Allen Temple Church. We have been hosting them for a long time.'

However Samkange made it clear that the relationship had broken down.
He said the Americans plan to go back home as soon as the case is over. He added that because the drugs have been taken by police as exhibits, they will not be distributed to the patients who badly need them.

Zimbabwe's broken health system is failing to contain the Aids epidemic and relies heavily on international and non-governmental organisations for help. Recently there were reports that HIV positive children who cannot get antiretroviral drugs now have to cross the border to South Africa to get medication.

If the allegations against the Centre are true, it will be disappointment for many who have supported the organisation which was founded by the late Lynde Francis, an ardent and respected Aids activist. She worked hard with other Aids charities to organise help for people living with Aids.

New treatment for rabies advances after successful phase 1 trial in India
BOSTON, Mass.—With the potential to save tens of thousands of lives each year, a new cost-effective rabies therapy developed by MassBiologics at the University of Massachusetts and the Serum Institute of India took an important step forward with positive results from a Phase 1 study. The recently completed study showed that a new monoclonal antibody (RAB-1) resulted in protective antibody levels in the serum of treated subjects equal to the current standard of treatment, which is often not available in the areas of the world hit hardest by rabies.

Details of the study were reported on September 14 at the American Society for Microbiology's 50th annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) meeting in Boston, Massachusetts in a poster presentation titled, "A Human Monoclonal Antibody to Rabies Virus Provides Protective Neutralizing Activity: Results of a Phase 1 Study," by researchers from MassBiologics; the Serum Institute of India in Pune, India; and King Edward Memorial Hospital (KEM) in Mumbai, India.
"We are very encouraged by the results from this trial," said Donna Ambrosino, MD, executive director of MassBiologics and a professor of pediatrics at the Medical School.

Subhash Kapre, PhD, of the Serum Institute of India, agreed saying, "The next step for clinical studies is already in the planning, and we are hopeful that this new therapy will have a major impact on rabies across the globe in the not too distant future."

The World Health Organization estimates that more than 10 million people are exposed to rabid animals each year, resulting in more than 55,000 deaths. Approximately 95 percent of human deaths from rabies occur in Asia and Africa. Untreated, the rabies virus causes an acute encephalitis that is fatal once symptoms appear; however the infection is preventable by prompt treatment following exposure, a procedure known as post-exposure prophylaxis (PEP) that involves administration of a rabies vaccine and rabies immune globulin (RIG) soon after exposure.

While the vaccine is often available, the preferred human rabies immune globulin (HRIG), which is derived from human blood, is expensive material and typically not available in developing countries. As an alternative to HRIG, equine immune globulin derived from horse serum is used in many parts of the world, but it is also scarce, expensive and can carry significant side effects. Too frequently, however, there is neither HRIG nor equine product available to treat all those in the developing world who are bitten by rabid animals.

To address the supply problems and side-effect issues, MassBiologics and the Serum Institute of India launched an effort to develop a monoclonal antibody (MAB) that could be used in place of HRIG. Pre-clinical testing of RABB1 showed that it neutralized all isolates available from a panel of rabies viruses. MassBiologics then partnered with the Serum Institute of India, which is one of the world’s largest manufacturers of vaccines, including a major supplier of the rabies vaccine, to develop the capacity to produce monoclonal antibodies in India, and advance RABB1 into clinical trials.

In the Phase 1 trial run at the KEM hospital, 74 healthy volunteers were randomized into several groups that either received escalating doses of RABB1 or of HRIG combined with vaccine. The RABB1 was well tolerated by all subjects, with no serious adverse side-effects caused by the MAB. Blood samples were then analyzed and showed the volunteers who received RABB1 and vaccine at a dose of 0.150 mg/kg had levels of rabies antibodies equal to or higher than the levels from those volunteers who had received the standard doses of HRIG and vaccine. The half life of RABB1 was 18-19 days.

Blood samples were also analyzed by the Kansas State Veterinary Diagnostic Laboratory to determine if antibodies present in the volunteers’ bloodstream could neutralize rabies virus in a cell-based assay using two different strains of virus. That data showed that volunteers who received RABB1 at 0.150 mg/kg with vaccine had similar or better protective serum levels when compared to those who received HRIG with vaccine.

Following the successful conclusion of this Phase 1 trial, the Serum Institute of India and MassBiologics are moving ahead in a clinical trial in India to evaluate the efficacy of RABB1 combined with vaccine compared to the standard of care for patients who have been exposed to potentially rabid animals. "Monoclonal antibodies can be produced in large quantities and at much lower costs than blood products, which could make this new therapy broadly available in Asia and India," Dr. Kapre said. "We remain optimistic that this program will eventually prevent thousands of deaths from rabies each year."

Human Papillomavirus Vaccination of Males: Attitudes and Perceptions of Physicians Who Vaccinate Females

The authors assessed US physicians’ attitudes and perceptions regarding potential human papillomavirus vaccination of males in a random sample of 2,714 pediatricians and family practitioners identified in administrative claims of a US health plan as HPV vaccinators of females.

Of the 595 pediatricians and 499 family practitioners who participated, most said they would recommend HPV vaccination to males ages 11-12 (63.9 percent), 13-18 (93.4 percent), and 19-26 (92.7 percent) years. Physicians agreed that males should be vaccinated to prevent transmission of genital and anal warts (52.9 percent strongly, 36.0 percent somewhat) and to protect females from cervical cancer (75.3 percent strongly, 20.8 percent somewhat). Respondents agreed that an HPV vaccine recommendation for males would increase opportunities to discuss sexual health with adolescent male patients (58.7 percent strongly and 35.3 percent somewhat). Most did not strongly agree (15.4 percent strongly, vs. 45.4 percent somewhat) that parents of adolescent males would be interested in HPV
vaccination for males, that a gender-neutral HPV vaccine recommendation would boost acceptance by adolescent females and their parents (19.6 percent strongly, 42.0 percent somewhat), or that a gender-neutral recommendation would improve current female vaccination rates (10.4 percent strongly, 26.0 percent somewhat).

“Physicians who currently vaccinate females against HPV supported the concept of vaccinating males for its benefits for both sexes. They agreed that a gender-neutral HPV vaccination recommendation would be appropriate with regard to public health and believed that it would increase opportunities for sexual health discussions, but were less sure that such a recommendation would change patient or parental attitudes toward HPV vaccination or improve current HPV vaccination efforts,” the authors concluded.

Gilead’s Quad HIV Pill Better than Best-Selling Atripla in 48-Week Study

In a small Phase II clinical trial, Gilead Sciences Inc.’s investigational fixed-dose, single-tablet “Quad” pill suppressed HIV better than its Atripla. Researchers presented the 48-week data on Monday in Boston at the 2010 Interscience Conference on Antimicrobial Agents and Chemotherapy.

The Quad regimen (elvitegravir, cobicistat, and Truvada [emtricitabine and tenofovir]) cut HIV to undetectable levels in 90 percent of the 48 patients taking it. In comparison, 83 percent of 23 patients taking Atripla (efavirenz, emtricitabine and tenofovir) achieved undetectable levels.

The Quad pill replaces one of Atripla’s components with elvitegravir, an integrase inhibitor. Cobicistat is used as a boosting agent and allows for once-daily dosing of the integrase inhibitor. In a separate 48-week trial, cobicistat was as effective a booster as Norvir was for atazanavir plus Truvada.

The Quad drug also had fewer side effects than Atripla, the conference heard. Three Quad recipients developed rash. Diarrhea was initially experienced by more Quad patients, but that balanced out after 48 weeks with Atripla-arm data. Earlier concerns about possible impaired kidney function later proved unwarranted.

“We’re pleased with the results, and it’s full-speed ahead,” said Steve Chuck, Gilead’s vice president of HIV therapies, referring to two larger, final-stage trials to be completed next year. “The data are very strong, very robust.”

Repeated Antibiotic Use Alters Gut's Composition of Beneficial Microbes, Study Shows
*ScienceDaily* (Sep. 13, 2010) — Repeated use of an antibiotic that is considered generally benign, because users seldom incur obvious side effects, induces cumulative and persistent changes in the composition of the beneficial microbial species inhabiting the human gut, researchers at the Stanford University School of Medicine have found.

By a conservative estimate, something like 1,000 different varieties of microbes coexist harmoniously within a typical healthy person’s gut, said David Relman, MD, professor of medicine and of microbiology and immunology at the medical school and chief of the infectious diseases division at the Veterans Affairs Palo Alto Health Care System. Relman is the senior author of a paper, which will appear online Sept. 13 in *Proceedings of the National Academy of Sciences*.

The study examined the effects of ciprofloxacin (trade name Cipro), an antibiotic that is widely prescribed for intestinal, urinary and a variety of systemic infections. In an earlier, short-term study, Relman’s group had concluded that people’s intestinal microbial communities seem to bounce back reasonably well within weeks after a five-day regimen of ciprofloxacin. This new study involved two courses of antibiotic administration, six months apart, and it revealed more-subtle, long-term effects of ciprofloxacin use—such as the replacement of multiple resident bacterial species by other, closely related varieties and the occasional complete eradication of a species.

The infrequent occurrence of easily visible side effects such as bloating and diarrhea from ciprofloxacin use has given rise to an assumption that the drug spares most beneficial gut-dwelling bacteria. Overall similarities between pre-regimen gut bacterial strains and their post-regimen replacements explain why such side effects aren’t typically seen after ciprofloxacin use. Still, the more nuanced differences between the pre-existing communities and those that appear in the wake of this repeated disturbance present a new set of problems, said Relman, who is also the Thomas C. and Joan M. Merigan Professor at the medical school. A bacterial species whose presence was lost or diminished may have been performing a valuable job—for example, secreting a protein that’s toxic to a particular
pathogen—that is shirked by its replacement. The abandoned function might not be noticed until, perhaps, years later when the pathogen in question invaded the person’s gut.

While the study’s findings shouldn’t be interpreted to mean that ciprofloxacin is dangerous and should be avoided, Relman said, they do raise questions about possible long-term effects of antibiotic administration, in addition to concerns about spurring the evolution of drug-resistant organisms. The new findings underscore the desirability of finding ways to pinpoint not just which bacteria have been lost or whose numbers were diminished by an antibiotic, but also which important beneficial functions performed by the patient’s gut microbial community as a whole have been impaired—such as signaling cells of the intestinal lining, which are constantly turning over, to maintain an appropriate barrier against ingested toxic compounds, or secreting anti-inflammatory substances that may prevent allergic or autoimmune diseases.

For this study, the Stanford scientists collected more than 50 stool samples from each of three healthy adult females over a period of 10 months. Then they used advanced, molecular techniques to count the number of different microbial species represented in each sample, as well as relative population sizes of the different species in that sample.

Twice during this 10-month period, the researchers perturbed their subjects’ gut ecosystems by giving them five-day courses of ciprofloxacin at a standard dose. During the first course, overall bacterial populations in each subject—which had previously waxed and waned but, on the whole, been quite stable—plummeted and remained depressed for about a week. Roughly one-third to one-half of the resident species’ populations declined, with some disappearing entirely. A few originally less-abundant species grew in number, as they filled in the ecological niche abandoned by bugs adversely affected by the drug.

Within a week after the first course’s completion, two of the three subjects’ internal microbial ecosystems had largely returned to a state fairly similar to that before the regimen, as measured by the broad classes to which the microbial constituents belonged. One subject’s overall ecosystem, however, still had not recovered even by that rough measure a full six months later.

The second course of antibiotic administration produced a stronger effect. “Even the one subject whose gut bacterial community fully recovered after the first ciprofloxacin course experienced an incomplete recovery after the second one,” said Relman. The communities in the other two subjects partially recovered from the second course, but never returned to their original state. In essence, each subject’s community of gut-dwelling microbes shifted to a new, “alternative” state and remained in that state for at least two months after the second antibiotic course had been completed. Thus, all three subjects experienced significant and lasting changes in the specific membership of their internal microbial communities at the end of the 10-month study period.

“Ecologists have found that an ecosystem, such as a wildlife refuge, that is quite capable of rebounding from even huge occasional perturbations—forest fire, volcanic eruption, pests—may yet be undone by too rapid a series of such perturbations,” said Les Dethlefsen, PhD, a research scientist in Relman’s lab and the study’s first author. “In the same way, recurring antibiotic use may produce a cumulative effect on our internal microbial ecosystems with potentially debilitating, if as yet unpredictable, consequences.”

“It’s as if your beneficial bacteria ‘remember’ the bad things done to them in the past,” said Relman. “Clinical signs and symptoms may be the last thing to show up.”

The precise counts of gut-dwelling microbes in this study were made possible by a new technique, pioneered in recent years by Relman and others. The older method—growing the microbes in culture—simply doesn’t work for many species and, even when it does, rare species are often swamped by more common ones and don’t get counted. The new technique reads short, telltale DNA snippets that distinguish microbes both from human cells and one from another. This allowed the Stanford researchers to assess both the total number of different microbial varieties and the relative size of each variety’s population.

Similar techniques now make it possible to assess, before and after antibiotic administration, the abundance in a patient’s gut of microbial genes known to code for important functions performed by one or more members of the patient’s gut community, Relman said. In the future, if it becomes known that a key function has been impaired, clinicians might perhaps restore that function by prescribing specific probiotics or nutrients that encourage the return of appropriate beneficial bugs.

**Journal Reference:**
Dana Willner, Mike Furlan, Robert Schmieder, Juris A. Grasis, David T. Pride, David A. Relman, Florent E. Angly, Tracey McDole, Ray P. Mariella, Jr., Forest Rohwer, Matthew Haynes. *Microbes and Health Sackler Colloquium: Metagenomic detection*
Kaposi's sarcoma occurring at higher CD4 counts
Michael Carter
Published: 16 September 2010
Over a third of cases of Kaposi’s sarcoma now occur in patients with a CD4 cell count above 350 cells/mm³, investigators from the US military report in the online edition of *AIDS*.

The study found that although rates of the AIDS-defining cancer have fallen since effective antiretroviral therapy became available, the proportion of cases that occur at higher CD4 cell counts has increased.

“Clinicians should be aware of these trends and watchful for the occurrence of Kaposi’s sarcoma despite robust CD4 cell counts”, comment the investigators.

Most cases of HIV-related Kaposi’s sarcoma occur when patients have a CD4 cell count below 200 cells/mm³. Although there is a large amount of evidence showing that rates of the cancer have decreased since effective antiretroviral therapy was introduced in the mid-1990s, it is not known whether Kaposi’s sarcoma will be seen at higher CD4 cell counts.

Therefore researchers from the US Military HIV Natural History Study reviewed the medical records of 5067 patients between 1985 and 2008.

Rates of the cancer were monitored in four time periods (1985-90; 1991-95; 1996-2001; 2002-2008). In addition, patients were divided according to whether their CD4 cell count was above or below 350 cells/mm³.

A total of 247 cases of Kaposi’s sarcoma were diagnosed. Compared with those seen between 1985-90, patients in the 2002-2008 time period had a 72% lower rate of the cancer (relative risk, 0.28; 95% CI, 0.16-0.47, p < 0.001).

In addition for each calendar period the investigators found that the rates of Kaposi’s sarcoma increased according to the amount of time patients spent with a CD4 cell count below 350 cells/mm³.

The investigators then looked at the CD4 cell counts of patients at the time their Kaposi’s sarcoma was diagnosed.

In 1985-90 a total of 18% of patients had a CD4 cell count above 350 cells/mm³ when their cancer was diagnosed. In 2002-2008 this had increased to 35%.

Analysis was then restricted to the 3422 patients who had received care after effective HIV therapy became available in 1996.

A total of 45 of these individuals developed Kaposi’s sarcoma.

Each 50 cell/mm³ increase in CD4 cell count reduced the risk of the cancer by 30%.

A CD4 cell count of less than 350 cells/mm³ (regardless of the use of HIV therapy) was associated with a significantly increased risk of Kaposi’s sarcoma (hazard ratio, 8.3; 95% CI, 3.4-20.2, p < 0.001).

“Our study demonstrates that although Kaposi’s sarcoma rates have declined during the HAART era and lower CD4 cell counts remain an important risk factor, a greater proportion of Kaposi’s sarcoma cases are now occurring at higher CD4 cell counts”, write the researchers.

Given these findings the investigators believe that it is important to see if starting HIV treatment at higher CD4 cell counts will reduce the risk of the cancer. “We found a suggestion of increased risk of Kaposi’s sarcoma among those not on HAART compared to those on HAART with CD4 cell counts of at least 350 cells/mm³”, they note.

Reference
Crum-Cianflone NF et al. Is Kaposi’s sarcoma occurring at higher CD4 cell counts over the course of the HIV epidemic? AIDS, advance online publication, September 4, 2010. DOI: 10.1097/QAD.0b013e32833f9fb8. (Link to abstract and full-text article).

Use of CCR5 Antagonist Does Not Explain Better CD4 Cell Recovery with Newer Antiretroviral Drugs

**SUMMARY:** HIV positive people using today’s state-of-the-art antiretroviral drugs are likely to achieve good CD4 cell recovery, but this cannot be attributed specifically to use of CCR5 antagonists such as maraviroc (Selzentry), according to a presentation at the 50th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC 2010) this week in Boston.

By Liz Highleyman
Antiretroviral therapy (ART) has improved markedly over the past decade, with medications that are more potent, more convenient, and less likely to cause serious side effects. In addition to new and
improved drugs in the non-nucleoside reverse transcriptase inhibitor (NNRTI) and protease inhibitor classes, the modern armamentarium includes 2 novel drug classes, integrase inhibitors and CCR5 antagonist entry inhibitors.

Some previous studies have suggested that CCR5 antagonists—a class that currently includes only 1 approved drug, maraviroc (Selzentry)—may produce larger CD4 cell gains than other types of antiretroviral drugs, but findings have not been consistent.

Marie Pichenot from University Hospital Tourcoing in France and colleagues aimed to assess the ability of a CCR5 antagonist to enhance CD4 cell recovery compared with other newer antiretroviral drugs.

The researchers performed a systematic review and meta-analysis of randomized clinical trials published in medical journals or presented at conferences since 2003 that looked at virological and immunological response to a new antiretroviral drug versus placebo in treatment-experienced patients. They included studies of maraviroc, the experimental CCR5 antagonist vicriviroc (now discontinued as an HIV candidate), the fusion inhibitor enfuvirtide (T-20, Fuzeon), the integrase inhibitor raltegravir (Isentress), the next-generation NNRTI etravirine (Intecence), and the 2 newest protease inhibitors, tipranavir (Aptivus) and darunavir (Prezista).

The investigators identified 10 studies that met the criteria for inclusion, representing a total of 6401 patients; 4 of these evaluated maraviroc. They collected information on baseline patient characteristics, rates of undetectable viral load, and changes in CD4 cell count at week 48 in groups receiving a new drug versus those receiving placebo—that is, compared with a background regimen without the new drug.

Results

- Use of newer antiretroviral agents was associated with superior CD4 cell response at week 48 compared with placebo (pooled difference in CD4 cell count +39 cells/mm3).
- However, use of a CCR5 inhibitor rather than another type of new drug did not explain this gain (P = 0.22).
- Male sex (P = 0.014) and initial genotypic sensitivity scores (a measure of drug resistance) of 0, ≤ 1, or ≤ 2 (P = 0.001, 0.0017, and 0.045, respectively) were associated with larger CD4 cell gains with new agents vs placebo.
- A higher rate of undetectable viral load in the placebo group at week 48—indicating that the background regimen was suppressing HIV by itself—was associated with a smaller difference in CD4 cell gains (P = 0.042).

Based on this analysis, the investigators concluded, "CCR5 [antagonists] do not allow a better CD4 cell recovery when compared to others new antiretroviral agents in treatment-experienced patients."

9/17/10

Reference


Older People with HIV Achieve Smaller CD4 Cell Gains Regardless of Antiretroviral Regimen

SUMMARY: HIV positive people age 50 and older may experience less robust immunological recovery—or smaller CD4 T-cell increases—after starting antiretroviral therapy (ART), no matter what type of regimen they take and even if they achieve good viral suppression, according to a large study described in the September 8, 2010 advance online edition of AIDS. These results, the investigators said, suggest that older people might benefit from starting treatment sooner.

By Liz Highleyman

Prior research has indicated that older HIV positive individuals tend to experience smaller CD4 cell gains after starting treatment, but past studies have produced mixed findings. Poor immune recovery may be due to age-related changes in the thymus and lymphoid tissues that produce T-cells or the cumulative effects of chronic inflammation and persistent immune activation.

To shed further light on this issue, Keri Althoff from Johns Hopkins University and colleagues performed a pooled analysis of medical records from participants in 19 prospective cohort studies that are part of the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD).

The analysis included 12,196 treatment-naive patients who started combination antiretroviral therapy between 1998 and 2008. The average age was 42 years, and about 20% were age 50 or older. Overall, they
had relatively advanced HIV disease, with CD4 counts below 250 cells/mm³; baseline CD4 counts did not differ according to age.

Nearly three-quarters started on an ART regimen containing a non-nucleoside reverse transcriptase inhibitor (NNRTI), while the rest received a ritonavir-boosted protease inhibitor (PI). About half changed their regimen during the follow-up period (48% of NNRTI recipients and 57% of PI recipients).

The investigators looked at how long it took to reach HIV viral load < 500 copies/mL and how long to achieve a CD4 cell gain of at least 100 cells/mm³ within the first 2 years of treatment.

**Results**

- People who started on a boosted PI were less likely to achieve a virological response, or viral load suppression (adjusted hazard odds ratio [HOR] 0.77, or 23% less likely).
- Patient age, however, did not have a significant influence on likelihood of viral suppression.
- Conversely, immunological response did not differ according to type of ART regimen.
- Here, however, increasing age was associated with decreasing likelihood of achieving a CD4 cell increase of 100 cells/mm³, regardless of initial regimen:
  - < 30 years: reference group for comparison;
  - 30-39 years: adjusted HOR 0.92, or 8% less likely;
  - 40-49 years: adjusted HOR 0.85, or 15% less likely;
  - 50-59 years: adjusted HOR 0.82, or 18% less likely;
  - ≥ 60 years: adjusted HOR 0.74, or 26% less likely.

Based on these findings, the study authors concluded, "We found no evidence of an interaction between age and initial antiretroviral regimen on virologic or immunologic response to [combination ART]."

"[D]ecreased immunologic response with increasing age may have implications for age-specific when-to-start guidelines," they suggested.

"[O]ur data do not currently support the use of specific [combination ART] regimens for specific age groups," they elaborated in their discussion. "However, given the impact of CD4 cell count on long-term survival, initiating [combination ART] at higher CD4 cell counts for older individuals may be useful given the decreased likelihood of a robust CD4 cell response with increasing age." 9/17/10

**Reference**


**Tulane University researchers find ancient roots for SIV**

The HIV-like virus that infects monkeys is thousands of years older than previously thought

The HIV-like virus that infects monkeys is thousands of years older than previously thought, according to a new study led by researchers from Tulane University.

Simian immunodeficiency virus (SIV), which is the ancestor to the human immunodeficiency virus (HIV), is between 32,000 and 75,000 years old and may even be more than a million years old, according to genetic analysis of unique SIV strains found in monkeys on Bioko, an island off the coast of Africa.

The research, which appears in the Sept. 17 issue of the journal *Science*, calls into question previous DNA sequencing data that estimated the virus' age at only a few hundred years.

"The biology and geography of SIV is such that it goes from the Atlantic Ocean to the Indian Ocean all the way to the tip of Africa. It would take many, many thousands of years to spread that far and couldn't have happened in a couple of hundred years," said virologist Preston Marx of the Tulane National Primate Research Center who led the study in conjunction with Michael Worobey, evolutionary biologist at the University of Arizona.
Marx tested his theory that SIV had ancient origins by seeking out DNA samples from monkey populations that had been isolated for thousands of years. His team collected bush meat samples from monkeys on Bioko, a former peninsula that separated from mainland Africa after the Ice Age more than 10,000 years ago.

Researchers found four different strains of SIV that were highly genetically divergent from those found on the mainland. They compared DNA sequences of the viruses with the assumption that they were tracking how both evolved over 10,000 years. The computer modeling showed the rate of mutation to be much slower than previously thought, indicating that virus is between 32,000 and 75,000 years old to have evolved to its current state. These dates set a new minimum age for SIV, although it is likely to be even older, Marx says.

The research has implications for HIV. Simian immunodeficiency virus, unlike HIV, does not cause AIDS in most of its primate hosts. If it took thousands of years for SIV to evolve into a primarily non-lethal state, it would likely take a very long time for HIV to naturally follow the same trajectory, Marx says.

The study also raises a question about the origin of HIV. If humans have been exposed to SIV-infected monkeys for thousands of years, why did the HIV epidemic only begin in the 20th century?

"Something happened in the 20th century to change this relatively benign monkey virus into something that was much more potent and could start the epidemic. We don't know what that flashpoint was, but there had to be one," Marx says.

Researcher Discovers New 'Anti-Pathogenic' Drugs to Treat MRSA

ScienceDaily (Sep. 17, 2010) — Menachem Shoham, PhD, associate professor and researcher in the department of biochemistry at the Case Western Reserve University School of Medicine, has identified new anti-pathogenic drugs that, without killing the bacteria, render Methicillin Resistant Staphylococcus Aureus (MRSA) harmless by preventing the production of toxins that cause disease.

Infections of MRSA are a growing public health problem causing 20,000 deaths per year in the U.S. alone. MRSA is the most prevalent bacterial pathogen in hospital settings and in the community at large. The problem has become increasingly severe due to the fact that the bacteria develop resistance to antibiotics.

Currently, there are only two antibiotics available to treat MRSA (vancomycin and linezolid) and strains are emerging that are resistant even to these two remaining antibiotics. As result, healthcare providers are running out of options to treat patients suffering from antibiotic-resistant infections, creating a dire need for alternative treatments and approaches.

"Staph bacteria are ubiquitous and normally do not cause infections, however, occasionally these bacteria become harmful due to their secretion of toxins," said Dr. Shoham. "We have discovered potential "anti-pathogenic" drugs that block the production of toxins, thus rendering the bacteria harmless. Contrary to antibiotics, these new anti-pathogenic drugs do not kill the bacteria. And since the survival of the bacteria is not threatened by this approach, the development of resistance, like that to antibiotics, is not anticipated to be a serious problem."

Dr. Shoham identified a bacterial protein, known as AgrA, as the key molecule responsible for the release of toxins. AgrA, however, needs to be activated to induce toxin production. His goal was to block the activation of AgrA with a drug, thus preventing the cascade of toxin release into the blood that can lead to serious infections throughout the body.

The screening for AgrA inhibitors was initially carried out in a computer by docking a library of 90,000 compounds and finding out which compounds would fit best into the activation site on AgrA. Subsequently, about one hundred of the best scoring compounds were acquired and tested in the laboratory for inhibition of the production of a toxin that ruptures red blood cells. Seven of these compounds were found to be active. Testing compounds bearing chemical similarity to the original compounds lead to the discovery of additional and more potent compounds. More than a dozen active compounds have been discovered by this method. The best drug candidate reduces red blood cell rupture to 12% of the value without the drug at a concentration of 10 µg/mL, without affecting bacterial growth.

"It is possible to inhibit virulence of MRSA without killing the bacteria," continued Dr. Shoham. "Such anti-pathogenic drugs may be used for prophylaxis or therapy by themselves or in combination with an antibiotic."
Bacteria Identified That May Lead to Inflammatory Bowel Disease in Certain Individuals

ScienceDaily (Sep. 17, 2010) — Certain bacteria that inhabit the intestine provide the environmental trigger that initiates and perpetuates chronic intestinal inflammation in individuals who are genetically susceptible to inflammatory bowel disease (IBD), a study led by Harvard School of Public Health researchers has found.

Inflammatory bowel disease results from a loss of homeostasis, or balance, between the immune system and the microbes that inhabit the intestine.

"In this study, we identified two microbes that instigate gut inflammation that leads to inflammatory bowel disease in mice," said lead investigator Wendy Garrett, assistant professor of immunology and infectious diseases at HSPH. "We show using both metagenomic and conventional culture techniques that an individual's genetic background influences what bacteria reside within his or her intestine. Several studies are currently underway examining the intestinal microbial communities of patients with IBD and we are looking forward to exploring the role of the Enterobacteriaceae we have identified in patients with IBD."

The study appears in the September 16, 2010, edition of Cell Host & Microbe.

IBD is a chronic inflammatory disorder that afflicts 1.4 million persons in the US and the incidence is rising around the world. Not only is IBD a devastating and debilitating chronic illness, it is also one of the three highest risk factors for the development of colorectal cancer. There are two principal forms of IBD: Crohn's disease and ulcerative colitis. Approximately 30,000 new IBD cases are diagnosed each year in the U.S.

Whether IBD is caused by individual species of bacteria or disruptions of entire microbial communities remains controversial, said senior author Laurie H. Glimcher, Irene Heinz Given Professor of Immunology at HSPH. "Our findings suggest that answer bridges both hypotheses—specific species of bacteria (Klebsiella pneumoniae and Proteus mirabilis) appear to work in concert with the indigenous gut microbial community to cause IBD."

How Bacteria Acquire Immunity: First Theoretical Description of Bacterial System to Silence Viral Genes

ScienceDaily (Sep. 16, 2010) — In a new study, Rice University scientists bring the latest tools of computational biology to bear in examining how the processes of natural selection and evolution influence the way bacteria acquire immunity from disease.

The study is available online from Physical Review Letters. It builds upon one of the major discoveries made possible by molecular genetics in the past decade—the revelation that bacteria and similar single-celled organisms have an acquired immune system.

"From a purely scientific perspective, this research is teaching us things we couldn't have imagined just a few years ago, but there's an applied interest in this work as well," said Michael Deem, the John W. Cox Professor in Biochemical and Genetic Engineering and professor of physics and astronomy at Rice. "It is believed, for instance, that the bacterial immune system uses a process akin to RNA interference to silence the disease genes it recognizes, and biotechnology companies may find it useful to develop this as a tool for silencing particular genes."

The new study by Deem and graduate student Jiankui He focused on a portion of the bacterial genome called the "CRISPR," which stands for "clustered regularly interspaced short palindromic repeats." The CRISPR contain two types of DNA sequences. One type—short, repeating patterns that first attracted scientific interest—is what led to the CRISPR name. But scientists more recently learned that the second type—originally thought of as DNA "spacers" between the repeats—is what the organism uses to recognize disease.

"Bacteria get attacked by viruses called phages, and the CRISPR contain genetic sequences from phages," Deem said. "The CRISPR system is both inheritable and programmable, meaning that some sequences may be there when the organism is first created, and new ones may also be added when new phages attack the organism during its life cycle."
The repeating sequences appear to be a kind of bookend or flag that the organism uses to determine where a snippet from a phage begins and ends. The CRISPR will often have between 30 and 50 of these snippets of phage sequences. Previous studies have found that once a bacteria has a phage sequence in its CRISPR, it has the ability to degrade any DNA or RNA that match that sequence—meaning it can fend off attacks from any phages that have genes matching those in its CRISPR.

"What we wanted to explore was how the history of a bacterium's exposure to phages influences what's in the CRISPR," Deem said. "In other words, how is an organism's previous exposure to viruses reflected in its own genome?"

From earlier published studies, Deem and He knew that phage sequences were added to the CRISPR sequentially. So, in a CRISPR system containing 30 snippets, the newest one would be in position one, at the front of the line. In another study in 2007, researchers examining the CRISPR of whole populations of bacteria noticed some statistical irregularities. They found that the likelihood of two different organisms having the same snippet in their CRISPR increased exponentially as they progressed away from position one. So, in the organism with 30 snippets, the phage gene in position 30 was the most likely to be conserved time and again across all the bacteria in the population.

To use the power of computers to examine why this happens, Deem and He needed a mathematical description of what was happening over time to both the bacterial and phage populations. The equations they created reflect the way the bacterial and phage populations interact via the CRISPR.

"Each population is trying to expand, and selective pressure is constantly being applied on both sides," Deem said. "You can see how this plays out in the CRISPR over time. There's a diverse assortment of genes in the first spacer, but the second spacer has been in there longer, so there's been more selective pressure applied to that spacer. Because bacteria that contain the dominant viral strain in their CRISPR are more likely to survive than those that don't, they tend to squeeze out their neighbors that are more vulnerable. At position N, the farthest way from position one, selection has been at work the longest, so the genes we find there were the most common and the ones that tended to afford the most overall protection to the organism."

In addition to interest from biotechnology firms, Deem said the workings of the CRISPR are of interest to drugmakers who are investigating new types of antibiotics.

The research was supported by the Defense Advanced Research Projects Agency.

Journal Reference:

Cardiac Imaging Breakthrough Developed
ScienceDaily (Sep. 17, 2010) — Cardiologists and surgeons may soon have a new tool to improve outcomes for patients requiring pacemakers, bypass surgery or angioplasties.

Research led by Dr. James White and his colleagues at The University of Western Ontario has led to a new imaging technique, which provides a single, 3D high-resolution image of the heart revealing both its vasculature and the presence of scar tissue within the muscle. This novel imaging was performed using a 3-T MRI at Western's Robarts Research Institute.

The findings are published on-line in the Journal of the American College of Cardiology: Cardiovascular Imaging.

Injuries to the heart, including heart attacks or viral inflammation, commonly result in permanent damage or scarring of its muscle. "We've known for some time that myocardial (heart) scar tissue can be imaged using MRI, but what we've now been able to do is to take this imaging to another level," explains Dr. White. "This is the first time we have been able to visualize myocardial scar and the heart's blood vessels at the same time. We are able to construct a three dimensional model of a person's heart to immediately understand the relationship between the heart's blood vessels and related permanent injury. This will help direct surgeons and cardiologists to better target the blood vessels that lead to muscle capable of responding to their therapy, rather than to muscle that is irreversibly diseased."

The technique works by first acquiring a 3D coronary image using a continuous infusion of a contrast called gadolinium, which makes the blood-pool light up brightly. The 3-T MRI takes images as this
contrast is infused into the blood stream, providing a high resolution, 3-D image of the heart showing coronary blood vessels. Scar tissue is slow to give up this contrast agent and its signal is therefore retained despite a washing out of contrast from the blood stream and normal tissues. A repeat image, performed 20 minutes later, highlights the heart’s scar, also in 3D. Because the two images are taken in the identical way using the exact same MRI pulse sequence, they’re already perfectly suited to be fused to one another. The result is a fused, 3D model of the heart that shows both the heart’s vessels and scar tissue.

The imaging technique was performed on 55 patients referred for either bypass surgery or a specialized pacemaker designed to improve heart function called Cardiac Resynchronization Therapy (CRT), demonstrating that the procedure was clinically feasible. The study was able to demonstrate that this novel imaging technique may be valuable in the planning of these vascular-based cardiac interventions. Dr White describes that in bypass or angioplasty procedures surgeons have to decide whether or not to open up blocked blood vessels, but if they can see there is scar in that region, no benefit will be expected. Similarly, CRT pacemaker leads delivered to regions of scarred heart muscle may prevent any benefit from this therapy.

Journal Reference:
James A. White, Nowell Fine, Lorne J. Gula, Raymond Yee, Mohammed Al-Admawi, Qi Zhang, Andrew Krahn, Allan Skanes, Anna MacDonald, Terry Peters, and Maria Drangova. Fused Whole-Heart Coronary and Myocardial Scar Imaging Using 3-T CMR: Implications for Planning of Cardiac Resynchronization Therapy and Coronary Revascularization. Journal of the American College of Cardiology: Cardiovascular Imaging, 2010; 3: 921–930 DOI: 10.1016/j.jcmg.2010.05.014

Dramatic rise in monkeypox
Posted by Bob Grant
[Entry posted at 31st August 2010 02:53 PM GMT]
Cases of monkeypox, a disease caused by a DNA virus closely related to smallpox and cowpox, have increased dramatically in rural villages in the heart of the Democratic Republic of Congo (DRC), according to researchers working in the war-ravaged African country.

Reporting their results online at PNAS, an international team of scientists found that within one area the average annual incidence of monkeypox between November 2006 and November 2007 increased by about 20 times compared to the average annual incidence recorded in the 5 years between 1981 and 1986, the last time scientists actively monitored the study population.

Though monkeypox is seldom fatal, the alarming increase in the DRC, where monitoring is sporadic at best, means that the disease has the potential to emerge as one that is more deadly and spreads faster, according to Anne Rimoin, the University of California, Los Angeles, epidemiologist who led the research team. "Each infection gives the virus the opportunity to evolve into a more virulent variant," Rimoin told The Scientist. "We're worried about what could happen. This study is a warning bell."

Anecdotal evidence has indicated for years that when global smallpox vaccination campaigns halted in the late 1970s, human monkeypox—to which the smallpox vaccine lends cross protection—was rare. Rimoin’s data strongly suggests that since smallpox vaccinations stopped, the incidence of monkeypox has been creeping back up, thanks in part to several species of wild animals serving as reservoirs. "The data do tell us that it appears that when smallpox immunization was common, monkeypox was acquired less often and transmitted less often," Don Burke, director of the University of Pittsburgh’s Center for Vaccine Research who was not involved in the study, told The Scientist. Indeed, Rimoin’s team found that people vaccinated for smallpox living in the study area had more than a 5-fold lower risk of monkeypox than unvaccinated individuals.
Though the original animal host of the virus that causes monkeypox is unknown, African squirrel, rat, mice, shrew, dormouse, and primate species are reservoirs. Transmission from animal to human likely occurs when people are bitten or come into contact with the blood or other body fluids of an infected animal. The human populations that Rimoin and her colleagues studied live near the tropical forest habitats of these animals and frequently eat them. With more migration from the countryside into cities and more so-called "bushmeat" starting to appear in markets in larger urban centers, such as DRC's capital Kinshasa, the monkeypox virus could spread beyond rural populations, Rimoin said. "It's only a matter of time that infected rodents are sold and distributed in larger cities."

In 2003, almost 100 people in the US contracted monkeypox after prairie dogs sold as pets came in contact with an infected shipment of African rodents, according to the US Centers for Disease Control and Prevention. None of the infected Americans died, but the incident "showed that the virus is capable of spreading to new animal reservoirs outside of central Africa," Rimoin noted.

But infection spreading from animals to humans is only part of the problem. The more worrying aspect of the disease's spread is human-to-human, or secondary, transmission, according to Burke. Rimoin said that her team wasn't able to track the rise in secondary transmission, but that she plans to conduct these studies soon. "When we see an increase that is so great, it suggests that human to human transmission may have also increased."

In addition, Rimoin said she plans sequence the virus samples she collected in DRC and compare them to samples collected in the 1980s to see if the monkeypox virus has been evolving in the last thirty years into become more transmissible or more virulent.

In the meantime, Rimoin suggested that the best way to stem the spread of the virus within the DRC is to launch educational campaigns that address proper handling of potential reservoir species and healthcare practices that prevent human-to-human transmission in the country. Though revisiting a widespread smallpox vaccination effort would almost certainly curb infection rates, she said that this would be virtually impossible. "At present the logistics of this are great and the expense would also be great," Rimoin said.

For now, monitoring of the situation is essential, agree Burke and Rimoin. "This is a perfect example of positioning ourselves to be able to predict and prevent at an early stage rather than waiting for a full blown epidemic," said Burke.


Comment:

Another Zoonotic Havoc
by Vinod Nikhra, [Comment posted 2010-08-31 12:20:13]

This may be just another epidemiological havoc, we are so much scared of now-a-days. As pointed out, monkeypox may have the potential to emerge as one that is more deadly and may spread outside African Continent. As known, the zoonotic diseases especially viral infection are known to culminate into a more virulent ones.

More analysis is needed about how and why the zoonotic diseases are crossing over to other species, human-beings in this case. Among other factors, of which environmental ones are more important, is the human genome is becoming more precarious?


Study Suggests Chronic Skin Eruption in HIV-Infected People is Related to Immune Deficiency and is Nonmalignant

“A CD8 cutaneous lymphoinfiltrative disease has been described in human immunodeficiency virus (HIV)-infected patients presenting with a severe erythroderma. ... Although some clinical features of this syndrome have raised the hypothesis of its malignant nature in initial observations, several studies have provided stronger support to the hypothesis that it is a reactive pseudotumoral process. ...  

“From 1995 through 2008, 8 HIV type 1 (HIV-1)-infected patients presenting with a chronic skin eruption, diagnosed as CD8 T cell infiltration of the skin, were studied. ...
“All patients showed diffuse infiltrated skin with superficial lymphadenopathy. A profound CD4(+) lymphocytopenia and eosinophilia were other major features. Histological and immunostaining analysis revealed a predominant dermal and epidermal infiltration by CD8(+) T cells belonging to the cytotoxic lineage, without evidence for a monoclonal status by polymerase chain reaction-based molecular analysis of lesional skin. A remission of skin symptoms occurred in all cases following highly active antiretroviral therapy, which paralleled the decrease of HIV-1 RNA load and the increase of CD4(+) peripheral blood absolute count. …

“Altogether, these results emphasize the reactive, nonmalignant nature of this syndrome and strongly support the coupling between HIV-induced immune deficiency and uncontrolled CD8 activation.”

**Study Suggests HAART Increases Viremia Clearance and Immune Response to Kaposi Sarcoma Herpes Virus in HIV-Infected Men Who Have Sex With Men**

“The objective of this study was to describe the effect of HAART on Kaposi sarcoma herpes virus (KSHV) antibody response and viremia among HIV-positive MSM. … This was a follow-up study of 272 HIV-positive MSM (including 22 with Kaposi sarcoma) who first initiated HAART between January 1996 and July 2004 in the Swiss HIV Cohort Study. … For each individual, two serum samples, one at HAART initiation and another 24 months later, were tested for latent and lytic KSHV antibodies using immunofluorescence assays, and for KSHV viremia using PCR. Factors associated with changes in KSHV antibody titers and viremia were evaluated. … At HAART initiation, 69.1 and 75.0% of patients were seropositive to latent and lytic KSHV antibodies, respectively. Seropositivity was associated with the presence of Kaposi sarcoma, older age, lower CD8 cell count and higher CD4/CD8 ratio. Prevalence of KSHV viremia at HAART initiation was 6.4%, being significantly higher among patients with Kaposi sarcoma (35.0%), and those with HIV viral loads 100 000 copies/ml (11.7%) or higher. At 24-month follow-up, geometric mean titers (GMTs) among KSHV seropositive patients increased and antibody seroprevalence was higher. Having Kaposi sarcoma and/or CD4 cell counts less than 50 cells/microl at HAART initiation was associated both with higher probability for antibody titers to increase (including seroconversion) and larger increases in GMTs. Only one of 17 viremic patients at HAART initiation had viremia at 24-month follow-up. … [The researchers concluded that] HAART increases KSHV-specific humoral immune response and clearance of viremia among HIV-infected MSM, consistent with the dramatic protection offered by HAART against Kaposi sarcoma.”

**Plague Researchers Race to Beat Bioterrorists**

ScienceDaily (Sep. 20, 2010) — Given the many pressing concerns of the day, fear of plague probably isn’t what causes most Americans to lose sleep. But for those whose responsibility it is to combat bioterrorism, plague is among the highest priorities. Those charged with that mission include scientists like medical researcher Steve Smiley, whose lab at the Trudeau Institute is working to develop a vaccine that will protect the public against weaponized forms of plague.

The Institute, which is dedicated to studying how the immune system responds to infectious diseases, is at the forefront of an international effort to protect the public against an ominous foe, whose very name conjures up images of widespread suffering and death.

Caused by the organism *Yersinia pestis*, plague is a severe and potentially deadly bacterial infection most often spread by rodents. Although rare in the United States, there have been outbreaks of plague in California, Utah, Arizona, Nevada, and New Mexico. Humans typically contract the disease from fleas that spread the bacteria from infected animals like rats, but plague can also spread from human to human, transported in the air through the coughs of the infected.

While plague is usually sensitive to antibiotics, the governments of the United States and Great Britain are concerned that weaponized plague would likely resist such treatment.

During the Middle Ages, resourceful armies hurled plague-infested bodies over castle walls to spread disease and fear, and it is widely believed this early form of biowarfare initiated the “Black Death,” the plague pandemic which decimated a third of Europe’s population. During World War II, the Japanese experimented with germ warfare by dropping plague-infested fleas on the Chinese. And the former Soviet Union’s biowarfare division produced bombs designed to release plague-causing bacteria into the air above American cities. A World Health Organization study concluded that the detonation of a plague “bio-bomb” over a city of five million could cause 150,000 cases of pneumonic plague, leading to 36,000 fatalities.
Small, natural outbreaks of plague continue to this day, and it remains among the deadliest of infectious diseases. Yet there continues to be no effective and reliable vaccine against the disease.

Both the United States and the United Kingdom are funding research aimed at developing an antibody-based vaccine against plague. Why antibodies? Antibodies are special proteins produced by the immune system in response to foreign invaders like bacteria, viruses and other microbes. After the immune system utilizes an antibody to fight off a dangerous pathogen, it retains a “memory” of the invader, so the relevant antibody can be rapidly reproduced should it encounter that same pathogen in the future. Many vaccines work by simulating exposure to a pathogen, thereby training the body to quickly generate the appropriate antibodies.

Several years ago, however, an enigma arose when the U.S. Army tested the leading plague vaccine candidate in two types of primates. Both produced similar amounts of antibody, but vaccination protected one type of animal much better than the other. Unfortunately, it’s not clear whether humans are more like the primates that were, or were not, protected. Most likely, humans will exhibit a range of responses, some similar to the one type of primate and some closer to the other.

In the current issue of the journal Vaccine, Dr. Smiley’s research group publishes data that may help unravel this enigma and provide a way to predict who will be protected with the plague vaccine being developed by the Army. In collaboration with the U.S. and U.K. militaries, as well as the Northeast Biodefense Center, they have shown that antibodies receive help from another part of the immune system when they protect against plague. Dr. Smiley’s laboratory has focused its efforts on pneumonic plague, the form of the disease that attacks the lungs. (Bubonic plague infects the lymph nodes; Septicemic plague infects the blood.)

Using a mouse model of pneumonic plague, they showed that antibodies work together with "cytokines" (proteins used by cells to communicate with one another) to control plague. There are many types of cytokines, each conveying distinct messages to cells that bear cytokine receptors on their surfaces. The two types of primates used in the plague vaccine studies almost certainly produced different amounts of cytokines. "This paper should encourage researchers to determine whether differences in cytokine production may explain why one was better protected than the other," said Dr. Smiley.

The Smiley lab is now working to produce an improved plague vaccine, one designed to leave the immune system with a memory that instructs it to produce both antibodies and the right mix of cytokines when it encounters plague.

Journal Reference:
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Salmonella creates environment in human intestines to foster its own growth
A study led by researchers at UC Davis has found how the bacteria *Salmonella enterica* — a common cause of food poisoning — exploits immune response in the human gut to enhance its own reproductive and transmission success. The strategy gives *Salmonella* a growth advantage over the beneficial bacteria that normally are present in the intestinal tract and promotes the severe diarrhea that spreads the bacteria to other people.

The findings are published in the Sept. 23 issue of the journal Nature.

"The human body normally has 10 times more microbes than human cells that help protect us against infection from disease-causing bacteria," said Andreas Bäumler, professor of medical microbiology and immunology at the UC Davis School of Medicine and the principal investigator of the study. "We have discovered *Salmonella’s* cunning trick that allows it to quickly take over and outgrow the beneficial microbes in our intestine."

All bacteria must generate energy in order to live and reproduce, either by respiration — which usually requires oxygen — or fermentation. Because essentially no oxygen is available in our intestines, the beneficial bacteria that reside there tend to use fermentation, which is less efficient than respiration for obtaining energy.

When people ingest *Salmonella*, it invades the surface of the intestine. Our immune system responds by producing oxygen radicals to kill the bacteria. Although some *Salmonella* bacteria are killed by this response, many more benefit: the oxygen radicals create a sulfur compound called tetrathionate, which *Salmonella* are able to use instead of oxygen for respiration.

Interestingly, tetrathionate has been used since 1923 by microbiologists as a way to promote the growth of *Salmonella* in biological samples containing competing microbes. But because tetrathionate
was not known to exist in living people, it was assumed prior to this study that this process had little relevance for food poisoning. Up until now, tetrathionate was believed to mainly exist naturally in decaying corpses or in thermal springs.

"Stimulating the host to produce tetrathionate enables Salmonella to 'breathe' in the intestine," said Sebastian E. Winter, who is a member of Bäumler's laboratory and lead author of the article. "This gives Salmonella a tremendous advantage over the gut bacteria that must grow by fermentation."

By stimulating an inflammatory response in the intestine, Salmonella also enhances its transmission to other hosts. The inflammatory response causes the severe diarrhea and vomiting that is the body's attempt to rid itself of the pathogenic bacteria, at the same time enabling Salmonella's spread.

The investigators used a combination of experiments with mouse models and test tubes to study the effects of intestinal inflammation on Salmonella and pinpoint the role of tetrathionate respiration. They also used novel techniques from the burgeoning field of metabolomics, which allowed them to measure metabolites in living animals.

Salmonella is frequently in the news as a source of food poisoning outbreaks, usually from eating poorly cooked or unhygienically prepared eggs or meat. Salmonella was the cause of a recall of about half a billion eggs last August and sickened more than 1,500 people. In that case, the ovaries of the hens were contaminated, so the inside of the eggs carried the bacteria and were not safe to eat unless thoroughly cooked. Reptiles such as turtles, lizards and snakes also carry the bacteria on their skin, sometimes causing illness in people who keep them as pets.

Salmonella infection, known as salmonellosis, causes diarrhea, fever, vomiting and abdominal cramps. Although most people recover after several days, it may be fatal, especially in the elderly, infants, and people with an impaired immune system.

For most cases of salmonellosis, antibiotic treatment is counterproductive, as it actually prolongs disease by further inhibiting the growth of beneficial bacteria. Finding that tetrathionate is important in human Salmonella infection opens up new avenues for research in finding an effective treatment for salmonellosis.

"Determining how Salmonella is so efficient in outcompeting resident beneficial bacteria is a critical first step in developing new drugs for treating food poisoning," said Bäumler, whose group is now pursuing this avenue of research. "We are hopeful that by targeting sulfur compounds we can stop the bacteria from establishing a foothold in the intestine."

**Scientists reveal structure of dangerous bacteria's powerful multidrug resistance pump**

The work may lead to the development of new antibiotics as well as the improvement of crop agriculture

LA JOLLA, CA – September 20, 2010 — A team at The Scripps Research Institute has detailed the structure of a member of the only remaining class of multidrug resistance transporters left to be described. The work has implications for combating dangerous antibiotic resistant strains of bacteria, as well as for developing hardy strains of agricultural crops.

"Now with our crystal structure, scientists can for the first time figure out exactly how this transporter works," said the study's senior investigator, Geoffrey Chang, Ph.D., associate professor in the Scripps Research Department of Molecular Biology. "This could lead to the design of drugs that evade or inhibit the transporter, or to reengineering the transporter to help some plants grow in soil they can't grow in now."

The protein described in the study, NorM, was found in the virulent bacteria Vibrio cholerae. V. cholerae causes cholera, a disease that affects the small intestine and is a common cause of death in developing nations. The NorM transporter is responsible for widespread resistance to ciprofloxacin and other fluoroquinolones (a broad-spectrum, inexpensive class of antibiotics) and to tigecycline, a new class of drug specifically designed to overcome that antibiotic resistance.

Importantly, NorM is a member of the multidrug and toxic compound extrusion (MATE) family that is involved in important biological functions across all kingdoms of life. These transporters defend plant, animal, and microbial cells by pumping out toxic chemicals before they can have any effect. In addition to antibiotic resistance, MATE transporters are associated with resistance to a commonly used diabetes drug, as well as resistance to anti-inflammatory and anti-arrhythmia agents. In plants, MATE transporters help to neutralize the acidity of soil, directly affecting crop yields worldwide.
"By showing how a key member of the [MATE transporter] family undergoes shape changes during the extrusion process, this work may lead to new ways to block the transporter, with possible applications in medicine and agriculture," said Jean Chin, Ph.D., who oversees this and other structural biology grants at the National Institutes of Health (NIH).

"Herculean Effort"

It took a "Herculean effort" to produce the high-resolution crystal structure of NorM, Chang noted. The researchers found it was difficult to produce enough protein to work with, and hard to purify the transporter in its natural state.

After the team found a way to produce and purify the protein, the scientists still needed to create crystals to be able to use a technique known as x-ray crystallography to solve its structure. In this method, scientists produce and purify large quantities of a protein that are crystallized. The crystal is then placed in front of a beam of x-rays, which diffract when they strike the atoms in the crystal. Based on the pattern of diffraction, scientists can reconstruct the shape of the original molecule. In this case, though, the NorM crystals were unusually fragile under an x-ray beam.

After many attempts, however, the research team succeeded in producing two crystal structures of the NorM transporter as it sat on the outside surface of V. cholerae. One showed the transporter by itself and the other provided a snapshot of how the pump is powered by sodium ions.

The NorM transporter normally sits, waiting, on the inside of the bacterial cell membrane for toxic chemicals—in this case antibiotics—that seep inside. The protein then changes shape in order to scoop the chemical up, and transport it back through the cell wall to the outside of the bacteria, keeping the bacteria safe from destruction.

The structure of this bacterial pump revealed a shape distinct from all other MDR transporter families, say co-authors Xiao He and Paul Szewczyk, graduate students at the University of San Diego, California, (UCSD) who worked with Chang to derive the structure. The pair also took the lead in the effort to verify the crystal structure—a process of labeling 16 different amino acids on the protein and confirming their three-dimensional position. This part of the effort took 18 months.

On the outside of the bacteria, the transporter looks like an upside down "V" shaped lampshade, He said, and the chemical to be removed presumably fits inside the narrow part of the structure. She adds that the research team is working to crystallize the transporter on the inside of the bacterium, as well as the structure with a chemical bound to it.

"Bacteria have a number of different transporter systems, so it is important to design antibiotics that will not be instantly pumped out," He noted.

With the atomic structure of NorM solved, the team continues to investigate other MATE transporters, including those found in plants and those that exist in human liver and kidney cells that can reduce the effectiveness of a wide variety of drugs.

New drug could help stop the spread of disease during cough: U of A research

What if there was a drug that could completely eliminate airborne disease transmission that occurs when someone coughs? Researchers at the University of Alberta believe they have found a way to achieve this.

The idea behind this work came from Malcolm King and his research associate Gustavo Zayas, who work in the Division of Pulmonary Medicine at the U of A's Faculty of Medicine & Dentistry. King and Zayas developed a drug that, when inhaled, would reduce or eliminate the amount of droplets, called bioaerosol, coming out of the mouth when a disease-infected person coughs. These airborne particles can stay in the air for minutes and sometimes even hours.

In order to help perfect this drug King and Zayas enlisted in the expertise of PhD student Anwarul Hasan and associate professor Carlos Lange, both from the Faculty of Engineering's mechanical engineering department. It was Hasan and Lange's role to find out how the size and amount of the cough-emitted droplets are affected by the new drug.

After five years of research, using a simulated cough machine, Hasan discovered how the new drug can manipulate the properties of the lung fluid to almost completely suppress the emission of droplets, a research first. This discovery provides a clear target for the new drug in its early phases of development. King and Zayas are moving forward to develop the drug in the form of a spray and plan to perform clinical trials in hopes that one day this drug could not only help stop the spread of a pandemic outbreak, but also protect nurses, doctors and other front-line health care professionals.

This research was recently published in the journal Non-Newtonian Fluid Mechanics and can be found here: http://dx.doi.org/10.1016/j.jnnfm.2010.07.005.
S.C. Prisons Brace for Lawsuit over Inmates with HIV


Despite a Wednesday deadline from the US Justice Department to change the practice, South Carolina says it will continue to segregate HIV-positive inmates. More than 400 inmates with HIV/AIDS are housed together at maximum security prisons in Columbia, including some who otherwise would not be in high-security facilities. Infected prisoners participate with other inmates in activities such as work, school, and faith-based programs, but they eat and sleep separately.

All state prisons “are safer from a public health perspective and a security perspective as a direct result of this program,” Corrections Department attorney David Tatarsky wrote in August, responding to the Justice Department.

Alabama, with 250 HIV-positive inmates, is the only other state to segregate prisoners living with the disease. Both states were criticized in a report released earlier this year by Human Rights Watch and American Civil Liberties Union (ACLU). That report called for all inmates to be housed together and for prisoners to be provided condoms and syringes to curb the spread of HIV. HIV-positive inmates lack access to the same programs and jobs as other prisoners and are wrongly stigmatized, the report argued.

“They also are prevented from participating in work-release programs, rendering them unable to shorten their sentences through credits.”

“That inevitably means that they serve longer sentences and are essentially being warehoused for no reason other than a medical condition,” said Margaret Winter, associate director of ACLU’s National Prison Project.

“Many inmates with HIV suffer disparate treatment from other similarly situated inmates without HIV,” the Justice Department noted in a June letter to South Carolina officials, giving them three months to make changes.

Alabama officials said they have not been threatened with a lawsuit. Neither South Carolina prison officials nor Department of Justice officials were available for comment Tuesday.

Anti-Circumcision Stance Must End to Fight HIV, Australian Researchers Say


In an opinion piece published this week, three researchers called on the Royal Australasian College of Physicians to reverse its policy recommending against routine circumcision of newborn boys.

“Circumcision of males is now referred to by many as a surgical vaccine against a wide variety of infections and adverse medical conditions over the lifetime,” said the article by Dr. Alex D. Wodak, director of the Alcohol and Drug Service at St. Vincent’s Hospital, Sydney; professor David Cooper, director of the National Center in HIV Epidemiology and Clinical Research; and Brian Morris, professor of Molecular Medical Sciences at the University of Sydney.

“A wealth of research has shown that the foreskin is the entry point that allows HIV to infect men during intercourse with an infected female partner,” they wrote.

Referencing large studies conducted in Africa, the World Health Organization cites “compelling evidence” that male circumcision reduces the risk of female-to-male HIV transmission “by approximately 60 percent.”

The procedure has not been shown to have a protective effect for men who have sex with men, the population that continues to account for most HIV cases in Australia. However, new infections among heterosexuals have been rising, according to the researchers, mirroring trends in North America and Western Europe.

In Australia, circumcision fell from favor in the mid-1970s as physicians concluded its risks outweighed its benefits. More recently, the proportion of Australian baby boys circumcised rose from 13 percent in 1998 to 19 percent in 2009, the study reported.

The authors called on Australia to resume paying for the procedure under the national health insurance program and to promote it across the region.


One in Four Youngsters 'Not Using Contraception'

**The Guardian (London)**, (09.20.2010) UK Press Association

A quarter of sexually active Britons under age 24 do not use any form of contraception with a new partner, according to results from a new worldwide survey by Marie Stopes International. That is an increase of 5
percent from 2009, suggesting that British authorities need to make sexual health and relationships education in schools a priority, said MSI, a sexual and reproductive health group.

The survey, released ahead of World Contraception Day (Sept. 26), included data from 5,223 respondents. British participants numbered 206 (100 male, 106 female) and answered online questions administered by market research firm GfK NOP.

Worldwide, 51 percent of males and 41 percent of females were not familiar with or were confused by contraceptive options, or said they did not know what form would be best for them. In Britain, the proportion was 32 percent, and 19 percent believed the “withdrawal method” is effective.

Personal hygiene was rated ahead of all other considerations, including contraception, when preparing for a date that could turn sexual.

Among UK youth who reported having unprotected sex with a new partner, 19 percent said they had been drunk; 16 percent said they had forgotten to use contraception; and 13 percent said their partner preferred not to use it. By age 18, 83 percent of Britons have had sex, according to government data, said Tracey McNeill, vice president of MSI’s UK and Europe branch.

“We are calling on the Coalition government to put sex and relationships education back on the agenda and ensure that all schools, including faith schools, teach a standardized curriculum,” McNeill said. “Where sex and relationships education is taught in conjunction with contraceptive information, more young people practice safe sex.”

For more information about the study, visit http://www.mariestopes.org/PressReleases/International/New_study_shows_young_people_need_clearer_information_about_contraception.aspx.

HIV Said to Differ in Blood, Semen

HIV in seminal plasma differs from HIV in blood plasma, according to a study led by researchers with the University of North Carolina (UNC)-Chapel Hill. The study examined in detail the genetic population of HIV, specifically the env gene for HIV’s envelope, in both blood and semen.

“If everything we know about HIV is based on the virus that is in the blood, when in fact the virus in the semen can evolve to be different, it may be we have an incomplete view of what is going on in the transmission of the virus,” explained Dr. Ronald Swanstrom, the study’s senior author and a professor at the UNC School of Medicine. Semen is the source of most HIV transmissions, the study notes.

The researchers mapped hundred of viruses in the 16 infected but therapy-naïve Malawian men, using single genome amplification. The results likely would not have changed with the inclusion of more men, said Dr. Stuart Shapiro of the Center for HIV/AIDS Vaccine Immunology. “It is an achievement they were able to do with 16 men,” he said of the expensive, time-consuming SGA technique.

In two subjects, the genetic diversity of blood plasma HIV was fully represented in the semen HIV. The research team concluded that there had been no compartmentalization in the seminal tract; rather, the populations had equilibrated.

A different phylogenetic pattern was detected in six subjects. Among these, semen HIV populations fully represented blood populations. However, there “was an additional feature of the viral populations in the semen of these subjects that distinguished them from the virus in the blood. In these subjects, sampling of the viral population in semen resulted in examples where identical or nearly identical sequences were observed. We term this phenomenon clonal amplification.”

In four of the 12 subjects with subtype C HIV-1, researchers found genetically distinct HIV populations in the seminal tract, indicating compartmentalization. The viral populations “indicated an autonomously replicating subpopulation that followed a distinct evolutionary pathway,” the study noted. “It compels us to ask the question, ‘What is making this virus different?’” Swanstrom said. The researchers do not believe the genetic differences observed affect infectiousness or lethality.


Sexual Health, Risk Behaviors and Substance Use in Heterosexual-Identified Women with Female Sex Partners: 2002 US National Survey of Family Growth

The phenomenon in which people engage in same-sex sexuality without espousing a sexual minority identity “has rarely been studied in women,” the authors wrote.
The current study used data from the 2002 US National Survey of Family Growth to compare a subset of women—heterosexuals ages 20 to 44 who had one or more female sex partners in the previous year—to bisexual, homosexual, and exclusively heterosexual women.

When compared to women who were exclusively heterosexual, heterosexual women reporting a past-year female sex partner were significantly more likely to: smoke tobacco (46 percent vs. 19 percent), binge-drink (34 percent vs. 11 percent), use marijuana (58 percent vs. 11 percent), and use cocaine (19 percent vs. 2 percent). “Substance use was high in this group overall, but they did not differ significantly from bisexuals on tobacco use or from homosexual or bisexual women on regular alcohol consumption,” the authors noted.

Most of the heterosexual women with a female partner in the past year had had only one such partner in their lifetime. They reported a median of 10 lifetime male sex partners compared to one to seven for other groups. Though similar to heterosexual women with less recent female sex partners and to bisexual women on some sexual risk measures, these women were more likely than any other group to have had a non-monogamous male partner (40 percent) or to have had sex while high (69 percent). Demographic differences did not explain the differences in sexual risk and substance use.

“Results suggest same-sex behavior in heterosexual-identified women is a marker for a substance use and sexual risk profile distinct from that of bisexual, lesbian or exclusively heterosexual women,” the authors concluded.

Zimbabwe Drops Charges Against Members of Medical Team

CNN.com, (09.23.2010)

Today in a Harare magistrate court, Zimbabwe’s government dropped its charges against six health workers who had been accused of dispensing HIV/AIDS medication without a license. The six—four Americans, a New Zealander, and a Zimbabwean—had maintained their innocence. The Americans are members of Allen Temple Baptist Church in Oakland, Calif., a predominantly black congregation that has supported an AIDS outreach in Zimbabwe since 2000. Mission members paid their own fare to Zimbabwe several times each year, and the government had even given them a farm, about 125 miles from Harare, where they care for patients and AIDS orphans. The team also operates a clinic in Harare. “The [attorney general] has been sympathetic to them because they are assisting the public,” said Jonathan Samukange, the defendants’ lawyer.

US CDC finds 19 percent HIV prevalence among MSM in 21-city survey

Kelly Safreed-Harmon
Published: 24 September 2010

Almost one in five participants in a 2008 survey of US men who have sex with men (MSM) were found to be HIV-positive, and almost half of the HIV-positive MSM were not aware of their status.

The US Centers for Disease Control and Prevention (CDC) has announced these and other findings from its periodic cross-sectional survey of urban MSM in the September 24th Morbidity and Mortality Weekly Report (MMWR). The survey collected information and biological specimens from 8,153 sexually active MSM in 21 major cities.

While an overall HIV prevalence rate of 19% was observed (95% confidence interval [CI], 18% – 20%), African-American survey respondents had a significantly higher rate of 28% (95% CI, 26% – 31%).

HIV prevalence ranged from 6% in Atlanta to 38% in Baltimore. Six other cities had HIV prevalence rates above 20%: Dallas, Houston, Miami, New Orleans, New York and San Francisco.

Among the 1562 men found to be HIV-positive, 44% either said that they did not know their HIV status or said that their last HIV test yielded a negative result (95% CI, 41% – 46%).

Further racial disparities were observed, with only 26% of HIV-positive white MSM unaware of their status (95% CI, 22% – 29%), but 59% of HIV-positive black MSM unaware of their status (95% CI, 55% – 63%). Hispanics and other non-whites also surpassed whites in this regard.

Higher rates of young HIV-positive MSM were unaware of their status as well. Seventy-five percent of HIV-positive MSM aged 18 – 19 fell into that category (95% CI, 55% – 89%), and 68% of those aged 20 – 24 did so (95% CI, 61% – 75%).

It is important to note that survey respondents were recruited from urban social venues identified by health department staff, and that two-thirds of those venues were bars and nightclubs. The findings therefore are not representative of the entire US population of MSM.
Nonetheless, the MMWR article raises concern about the HIV epidemic's persistence in US MSM populations in the face of intensive targeted HIV prevention campaigns.

Five cities that were included in both the most recent survey and the preceding survey (2004/2005) were compared to each other in the MMWR article. While trends for individual cities varied, there were no major overall differences in relation to either HIV prevalence or awareness of having HIV.

The MMWR article also called attention to current efforts to encourage HIV testing, noting that 55% of HIV-positive MSM who did not know their status had not taken an HIV test within the preceding twelve months. The CDC recommends HIV testing on an annual basis or more frequently for sexually active MSM.

“This finding suggests that increased efforts to educate MSM and health-care providers about HIV testing guidelines and to reduce barriers to HIV testing for MSM are necessary,” the authors concluded.

They also observed that since 45% of HIV-positive MSM who did not know their status had fulfilled the CDC testing recommendation, shorter testing intervals may be advisable for some MSM.

The CDC has estimated that nearly half of the more than one million HIV-positive people in the United States are MSM. CDC surveillance also suggests that MSM are the only major HIV risk group still continuing to experience an increasing number of infections.

In a statement about the MMWR update, Gay Men’s Health Crisis (GMHC), one of the largest community-based AIDS organizations in the United States, called for new HIV prevention approaches that address homophobia as a driver of the MSM epidemic.

“We should recognize anti-gay prejudice as a public health threat that has public health effects,” said GMHC representative Sean Cahill. “The CDC and state and local health departments must challenge anti-gay stigma and promote acceptance of gay people, including encouraging parents to accept and love their gay sons. Expanded [HIV] testing campaigns are not enough.”

GMHC also emphasized the link between high HIV prevalence among young MSM and young people’s sexual health more generally.

“Nearly 20 million Americans got a sexually transmitted disease last year, and half of them are 15 to 24 years old,” Cahill said. “We must get real about providing age-appropriate sexual health education in schools.”

Reference

GRACE Trial Finds Women Respond as Well as Men to HIV Treatment, but More Likely to Stop Therapy

SUMMARY: HIV positive women and men taking antiretroviral therapy (ART) containing boosted darunavir (Prezista) had statistically similar treatment response rates, with the slightly poorer outcomes among women probably due to their higher likelihood of discontinuing therapy, according to a report of findings from the GRACE (Gender, Race And Clinical Experience) study published in the September 21, 2010 Annals of Internal Medicine. GRACE showed that it is possible to recruit and conduct a clinical trial with a large number of women, many of them socioeconomically disadvantaged, but the 33% dropout rate suggests additional efforts are needed to retain women in such studies.

Below is an excerpt from a press release issued by Tibotec, which produces darunavir, describing the GRACE study and its findings.

Data from Landmark Study Evaluating Gender Differences in Response to an HIV Therapy Published in Annals of Internal Medicine

The GRACE study has significant implications for inclusion of women in clinical trials

Titusville, NJ—September 20, 2010—Data from the GRACE (Gender, Race And Clinical Experience) study will be published in the September 21st issue of the Annals of Internal Medicine. GRACE is the largest-ever study of treatment-experienced adult women with HIV-1 to examine gender differences in response to HIV therapy. Sponsored by Tibotec Therapeutics Clinical Affairs, a division of Centocor Ortho Biotech Services, LLC, the GRACE study enrolled 67 percent women, demonstrating that it is possible to recruit large numbers of women into U.S.-based HIV treatment studies. The company has launched www.TheGraceStudy.com to share learnings from the GRACE study and other information for women living with HIV.

Among patients who completed the study, there were no significant differences in treatment responses between men and women who were given Prezista (darunavir) 600 mg coadministered with 100 mg ritonavir twice daily, as part of combination therapy. The GRACE study was designed in partnership with the HIV community and used unique strategies to encourage women living with HIV to
participate in the trial. However, even with its novel enrollment strategies, the study showed a higher discontinuation rate among female study participants—making the overall response rate lower among women than among men, and shedding light on the need for additional efforts to retain diverse populations in clinical studies.

"Better representation of women in clinical trials is essential for generating accurate information on the efficacy and safety of medicines and, ultimately, guiding treatment decisions," said Judith Currier, MD, Professor of Medicine, Associate Division Chief, Division of Infectious Diseases, University of California, Los Angeles, Director of the Clinical Trials Unit, UCLA Center for Clinical AIDS Research and Education (CARE), and primary investigator in the GRACE study. "The GRACE study has the potential to shape how future studies are conducted because it addressed the social and economic barriers that historically have prevented women from participating in clinical research. It also showed that we have a long way to go before we can fully overcome these barriers."

In the United States, women account for an increasing proportion of people living with HIV/AIDS, including more than one quarter of new diagnoses. Yet despite their growing numbers, women have been under-represented in HIV treatment studies. This may be due to recruitment and retention challenges including family commitments, time constraints with jobs, and other socioeconomic factors. These observations have been noted in clinical trials of other therapeutic areas, including heart disease and cancer, suggesting that difficulties in recruiting women are not specific to HIV clinical trials. As a result of having a low number of women in these studies, gender-based conclusions are limited, and there remains a gap in clinical data.

"Unlike most studies of HIV medicines, GRACE was specifically designed and powered to assess gender differences in response to treatment," said Dr. Currier. "We took steps that have never before been used to make sure our study population was reflective of the demographics of women with HIV in the United States."

**GRACE Study Design and Results**

GRACE was a multi-center (65 sites), open-label Phase 3b trial that compared the efficacy, safety, and tolerability of the protease inhibitor Prezista (600 mg) boosted with a low dose of ritonavir (100 mg) twice a day, in combination with an investigator-selected optimized background regimen for 48 weeks in men (n=142) and women (n=287).

The study was designed to enroll a high proportion of North American, treatment-experienced women that was reflective of the distribution and demographics of women with HIV in the United States. Trial sites were selected to correspond with the geographic distribution of women with HIV, with the majority of sites located in the Northeastern (16 sites) and Southeastern (29 sites) United States. Study sites were initially required to enroll three women before enrolling a man, and thereafter, each site was required to maintain at least 70 percent female enrollment. Men could only be enrolled if their addition did not compromise the 70 percent female quota.

GRACE participants also received support to cover costs associated with study participation, including assistance for travel, childcare and food vouchers, and study sites could access grants for patient support activities such as lunch-and-learn sessions and patient support groups for ongoing education and camaraderie.

At the end of the study period, there were no statistically significant differences in virologic response (defined as a viral load of < 50 copies/mL) rates between women and men. Results from an intent-to-treat time-to-loss of virological response analysis (ITT-TLOVR) showed that 50.9 percent of women reached an undetectable viral load (< 50 copies/mL) at week 48 compared with 58.5 percent of men (p=not significant). These figures included men and women who had discontinued the study. When treatment discontinuations for reasons other than virologic failure were discounted, 73 percent of women and 73.5 percent of men reached an undetectable viral load (p=not significant).

Discontinuation rates driven by reasons other than virologic failure were 32.8 percent for women versus 23.2 percent for men. Loss to follow-up was the most common reason for discontinuation. There were no clinically relevant differences in safety or tolerability between women and men. In adult patients receiving a Prezista/ritonavir-containing regimen, the most common treatment-related adverse events (≥ 2 percent) reported of at least moderate to severe intensity (≥ Grade 2) were nausea (5.2 percent for women and 2.8 percent for men), diarrhea (4.5 percent for women and 4.9 percent for men) and rash (2.1 percent for women and 2.8 percent for men).

Additional analyses were conducted as part of the GRACE study, including a sub-study examining efficacy and safety differences in response to race, as well as an immunology sub-study.

Full prescribing information for darunavir is available at [www.Prezista.com](http://www.Prezista.com). 9/24/10
New HIV Infections Fall Worldwide, but Economic Crisis Threatens Further Progress

**SUMMARY:** Progress has been made in the fight against AIDS, with more than 20 heavily affected countries seeing at least a 25% reduction in new infections, according to a recent report issued by UNAIDS. But participants at a UN meeting this week in New York City to discuss the status of the Millennium Development Goals (MDGs) emphasized that much remains to be done by the 2015 deadline—including virtual elimination of mother-to-child HIV transmission—and resources must be found despite the ongoing global economic downturn.

By Liz Highleyman

The new UNAIDS report provides an overview of 6 key aspects of the response to HIV/AIDS today:

1. New HIV infections are falling.
2. More than 5 million people are on HIV treatment.
3. HIV prevention works.
4. Virtual elimination of mother-to-child transmission is possible by 2015.
5. Criminalization is challenging the AIDS response.
6. Investing for AIDS is a shared responsibility.

The full report is available online.

New HIV infections are steadily declining around the world, and 22 of the most affected countries in sub-Saharan Africa have reduced HIV incidence by more than 25%, according to the report. Some countries with large epidemics are leading the way in reducing new infections—including Cote d'Ivoire, Nigeria, South Africa, Zambia, and Zimbabwe—but the number of infections continues to rise in Eastern Europe and Central Asia.

Globally, the report continues, the rate of new HIV infections still outstrips advances in providing antiretroviral therapy, with 5 people newly infected for every 2 people who start treatment. About 40% of these new infections are among young age 15-24 years, and women continue to be disproportionately affected, comprising nearly 60% of people living with HIV in sub-Saharan Africa.

Continued progress in addressing the epidemic will require that wealthier countries and private donors not only maintain their current level of funding, but increase their support—"a very difficult issue these days given the crisis, given the budget constraints for donors," said Global Fund executive director Michel Kazatchkine.

Much discussion at this week's MDG meeting focused on ongoing efforts to integrate HIV services into general maternal and child health efforts. Some advocates claim that this de-emphasizes HIV/AIDS and will spread resources too thin, while some policy experts counter that it is not efficient or sustainable to address global health one disease at a time.

"You cannot really separate AIDS from sexual and reproductive health or maternal health," said Kazatchkine, Voice of America reported. "Over 50 percent of deaths in women between the ages of 15-49 in Africa are from AIDS."

In addition to "virtual elimination" of mother-to-child HIV transmission—made possible by expanded antiretroviral therapy for HIV positive pregnant women—the MDGs, set in 2000, also include reducing extreme poverty by half, doubling the number of people with access to clean water, reducing maternal mortality by three-quarters, and ensuring that all children receive a primary school education.

U.S. president Barack Obama—who attended the MDG summit—was chided for failing to do enough to address the global epidemic, echoing criticism he and other leaders of other industrialized countries received this past summer at the XVIII International AIDS Conference in Vienna.

UN Secretary-General Ban Ki-moon has said he hopes to get commitments for an additional $45 million in aid during the meeting. 9/24/10

Sources

1. UNAIDS, [MDG 6: Six Things You Need to Know about the AIDS Response Today](http://unaidstoday.org).
2. UNAIDS Today blog, [September 17-22, 2010](http://unaidstoday.org).
A biological solution to animal pandemics
EUREKA project E4104 ECOPROMAT has developed a novel and environmentally-friendly type of matting for use in protection against the spread of contagious animal diseases such as avian influenza, and for routine hygiene in animal and food production. Soaked with disinfectant solution, the matting can be used for disinfecting vehicle tyres, and the shoes and boots of personnel. As it is made of 100% natural fibres, it is highly absorbent to disinfectant solution; it is also fully biodegradable and therefore avoids the high disposal costs of synthetic alternatives. The under-surface is made of densely woven fabric for strength, and impregnated with natural resin to prevent seepage of disinfectant into the ground, or dilution of disinfectant by ground water.

Outbreaks of contagious animal diseases like avian flu, foot-and-mouth disease and bovine spongiform encephalopathy (BSE), cause national and regional public health authorities take extensive steps to prevent these diseases from spreading. The economic costs of such outbreaks are hard to estimate, but they can cause major disruption to agricultural production and food distribution, also environmental challenges in disposal of infected animals and contaminated materials; plus widespread public anxiety.

Stopping the spread of disease
Most animal diseases are spread on clothing, footwear or farm tools, equipment or the tyres of vehicles visiting farms with infected animals. When public health measures are imposed, personnel are required to pass through disinfection barriers in order to stop the transportation of bacterial or viral particles. The various methods in use until now all have disadvantages. Requiring people and vehicles to pass through a shallow bath of disinfectant solution or a trough of sawdust or wood chips soaked in disinfectant is cumbersome, costly and requires labour for replacement. Another approach is a mat with an outer polyester layer, an absorbent layer made of polyurethane and a third PVC layer to prevent disinfectant from penetrating into the ground; or a nylon fibre mat backed with nitrile rubber. However the raw materials used in those mats make disposal difficult and costly, requiring special treatment plants for degradation.

Natural fibres are the solution
The new matting developed by the ECOPROMAT partners is also composed of three layers, but uses only natural materials. The lowest layer is a densely woven hemp, flax or jute fabric chosen for its toughness, resistance and flexibility, and stitched in hemp or jute fibres. This layer is finished by impregnation with natural resins, which prevent seepage of the disinfectant into the ground, and also prevent dilution of the disinfectant by absorption of ground water. The central layer of the mat is highly absorbent, non-woven material which is significantly more hygroscopic than the synthetic alternative. The upper layer is woven, needle-punched jute fabric, which is protective and durable to protect the central reservoir from pressure e.g. from vehicles driven over it. Dr Jerzy Mankowski of the Polish Institute of Natural Fibres & Medicinal Plants explains that unlike the synthetic alternatives, matting made of flax and hemp fibres is completely biodegradable and environmentally friendly.

The Institute of Natural Fibres, which led the ECOPROMAT project, was partnered by the German company, Bioformtex from Zehdenik. The main task of the Institute was to develop the three-layer non-woven product with appropriate strength, thickness and weight, to allow for proper absorption of disinfectant solution but not allowing penetration of the disinfectant into the ground. Various combinations of flax and hemp were tested to determine the mechanical and needling parameters affecting the tensile strength and recovery potential; to determine the most suitable and cost-effective textile material for the lowest layer.

Bioformtex developed the dense, non-woven central layer and the needle-punched jute upper layer. It also investigated the addition of disinfectant in powder form to the nonwoven layer during production, and developed composting accelerators to aid degradation of the natural resin in the matting.

Into production
The matting is now manufactured by Bioformtex and by another company not involved in the original project: Lenkon, from Poland. Total mat production has reached about half a million square metres per year. The Polish animal medicines company BIOWET Drwalew, which supplies disinfectants and related equipment, is supplying the matting to commercial users. Return on the project investment is anticipated within 4-5 years.

The matting is covered by Polish and European patents, and is being used in poultry, pig and cattle production units, dairies, meat processing plants and slaughterhouses, apiaries, and food processing
It is also used for more general antibacterial hygiene, e.g. mushroom-growing cellars and greenhouses; agricultural research centres, border crossings and quarantine areas.

The initial cost of the new matting is low—between €10-12 per square metre, which is a significant saving on synthetic matting at €15-20 per square metre. Cost saving also results from the biodegradability of the new natural-fibre matting, which means that contaminated matting can be disposed of much more readily and cheaply than the synthetic alternatives.

Microbiologists Find Source of Fungus’s Damaging Growth

ScienceDaily (Sep. 22, 2010) — Candida albicans, a fungus that kills more than 10,000 people with weakened immune systems each year, grows more dangerous as it forms and extends long strands of cells called hyphal filaments. In a paper published this month, UT Health Science Center San Antonio microbiologists describe a key factor involved in this damaging growth.

This finding may eventually lead to targets for antifungal strategies, the scientists said. Patricia Carlisle, a Ph.D. student at the Health Science Center, and David Kadosh, Ph.D., assistant professor of microbiology, found that Ume6, a key transcriptional regulator, targets a specific hyphal filament-development mechanism. “No one knew that Ume6 was involved in directing this process,” Dr. Kadosh said. “Perhaps we can learn how to mute its signals.”

Transcriptional regulators direct the conversion of DNA (deoxyribonucleic acid) into RNA copies. Copies of RNA (ribonucleic acid) are translated into proteins that carry out activity.

Bugs impact

Candida albicans preys on hospitalized critical care patients, HIV/AIDS patients, cancer patients and others with weakened immune systems. It is the fourth-leading cause of hospital-acquired infections in the United States.

“The forming of hyphal filaments is very important in tissue invasion and other activities,” Dr. Kadosh said.

The findings were featured as a Spotlight article in the September issue of Eukaryotic Cell, a journal of the American Society for Microbiology.

Journal Reference:
P. L. Carlisle, D. Kadosh. Candida albicans Ume6, a Filament-Specific Transcriptional Regulator, Directs Hyphal Growth via a Pathway Involving Hgc1 Cyclin-Related Protein. Eukaryotic Cell, 2010; 9 (9): 1320 DOI: 10.1128/EC.00046-10

Drug Against AIDS Could Be Effective Against Herpesvirus

ScienceDaily (Sep. 23, 2010) — Scientists at the Institute for Research in Biomedicine (IRB Barcelona) headed by the coordinator of the Structural and Computational Biology Programme, Miquel Coll, have published a new study that demonstrates that raltegravir, the drug approved in 2007 for the treatment of AIDS that is sold by Merck under the name Isentress, cancels the function of an essential protein for the replication of one kind of herpes virus. This study, published in the journal Proceedings of the National Academies of Sciences (PNAS), is the first step towards the development of a drug against the entire Herpesviridae family.

“These results have a clear medical impact for three reasons,” explains Miquel Coll, also a CSIC research professor. "First, humans do not have the viral protein that is affected, thus this would allow a highly specific drug that does not show the secondary effects that other drugs may have. Second, the inhibitor is not toxic for humans when administered at therapeutic concentrations because it is already on the market and thus toxicity tests are facilitated; and third, we have data that indicate that all herpes viruses have this protein. Therefore, it could be a valid target against all Herpesviridae.”
Herpesviruses include pathogens such as herpes simplex 1 and 2, the virus that causes chickenpox otherwise known as zoster virus, the Epstein-Barr virus -associated with several types of cancer -, the roseola virus, the cytomegalovirus and the herpes virus associated with Kaposi sarcoma -in AIDS patients -. The human cytomegalovirus (HCMV), on which the study was performed, causes neurological defects in 1% of neonates in developed countries. It also produces retinitis that deteriorates into blindness in 25% of subjects with AIDS, defects in the brains and central nervous systems of young adults, inflammation of the colon -also in those with AIDS -, mononucleosis and serious diseases of the throat. Although 90% of adults carry HCMV, this virus is opportunistic, acting in people with weakened immune systems such as in cancer and AIDS patients, recipients of organ transplants and neonates.

Blocking viral replication
To replicate, the herpes virus enters the nucleus of a cell where it uses the cell machinery to copy its DNA several times into a single large chain. Once this copy has been made, acts a complex called terminase, formed by three protein subunits. The terminase cuts the new DNA into small fragments, the size of a single viral genome, and introduces these into empty shells (capsids) that have developed in the cell nucleus. Then, the new viruses leave the cell to continue infection. The researchers resolved the 3D structure of one part of the terminase and when they observed that it resembled the integrase of the AIDS virus, for which drugs are available, they tested it against the herpes virus protein. Thus they discovered that raltegravir acts on the subunit UL89 of the terminase and cancels the scissor function, which is required for viral replication.

The assays were performed directly on the protein in test tubes. "Now we must do the assays on whole infected cells, improve the effect of the drug and validate that it is also effective for other kinds of herpes viruses," explains Miquel Coll, whose lab has patented this second application for raltegravir. To resolve the 3D structure of the target protein, the scientists have used a state-of-the-art high-performance protein expression technique, with the collaboration with Darren Hart's group at EMBL in Grenoble, where 18,000 clones or different fragments of the protein have been tested. They have also used the Grenoble synchrotron to obtain the structural data. The study has lasted five years and forms part of the European project SPINE-2 complexes.

Journal Reference:

Non-Stick Coating of a Protein Found in Semen Reduces HIV Infection
ScienceDaily (Sep. 23, 2010) — A non-stick coating for a substance found in semen dramatically lowers the rate of infection of immune cells by HIV a new study has found.

The new material is a potential ingredient for microbicides designed to reduce transmission of HIV, a team from the University of Rochester Medical Center and the University of California, San Diego reports in a forthcoming issue of the Journal of Biological Chemistry.

The coating clings to fibrous strings and mats of protein called SEVI-for semen-derived enhancer of viral infection—which was first discovered just three years ago. SEVI seems to attract the virus and deposit it onto the surface of T-cells, components of the immune system that are the primary target of HIV infection, and may play an important role in sexual transmission of HIV.

Like the fibrous strings that bind senile plaques associated with Alzheimer's disease, SEVI is a kind of protein superstructure called an amyloid.
Jerry Yang, associate professor of chemistry at UC San Diego and his research group developed non-stick coatings for amyloids as a potential treatment for Alzheimer's disease in 2006. Their idea was to minimize damage by preventing amyloid proteins from interacting with other molecules in the brain.

When this new amyloid, SEVI, was discovered in 2007, Yang was interested in testing whether the coating strategy might interfere with SEVI's role in promoting HIV infection.
Yang's group teamed up with a researchers led by Stephen Dewhurst, chair of the microbiology and immunology department at the University of Rochester Medical Center, who studies HIV.
"We tested one of our molecules out on SEVI and found it was able to stop SEVI-enhanced infection of HIV in cells," Yang said. "It works in semen too. Something in semen enhances viral infection—SEVI and maybe other things. This molecule stops that."

When the researchers added the molecule that forms non-stick coatings to a mix of SEVI, virus and cells, rates of infection dropped to levels observed when SEVI was absent. They saw a similar effect with
semen as well, evidence that this potential microbicide supplement works to inhibit infection within a mixture of proteins and other molecules found in seminal fluid.

The coating molecule is a modified form of thioflavin-T, a dye that stains amyloid proteins. It fits in between the individual small proteins that cluster to form SEVI and blocks SEVI's interactions with both the virus and the target immune cells.

"Other people have tried to do the same thing by targeting the virus or the cells it infects. What we do is target the mediator between the virus and the cells," Yang said. "By neutralizing SEVI, we prevent at least one way for HIV to attach to the cells."

The new molecule has another advantage. Unlike many current microbicide candidates aimed at reducing HIV infection, this one doesn't cause inflammation in cervical cells.

"Recent studies have shown for the first time that a topical microbicide gel can protect women from HIV-1 infection. This is a huge step forward but not a perfect solution. We need to figure out ways to further improve protection—and our studies suggest one way of doing so," said Dewhurst, who is the corresponding author of the report. "It may be possible to produce a next-generation microbicide that includes both an antiviral agent, as has been used in the past, and an agent that targets SEVI. We're very excited about exploring this idea."

Journal Reference:


One in Five Gay, Bisexual Men in US Cities Have HIV

Reuters, (09.23.2010) Julie Steenhuysen

A CDC study of men who have sex with men (MSM) in 21 major cities found nearly one in five are infected with HIV, and 44 percent did not know it.

CDC researchers tested 8,153 MSM participating in the 2008 National HIV Behavioral Surveillance System. Overall, 19 percent were HIV-positive.

The highest infection rate, 28 percent, was found among black MSM. Eighteen percent of Hispanic MSM were infected, as were 16 percent of white MSM.

Lower levels of income and education were associated with higher rates of HIV infection. Among other findings:

• Among MSM with HIV, 59 percent of blacks were unaware of their infection, compared to 46 percent of Hispanics and 26 percent of whites.
• MSM under age 30 had lower HIV prevalence than older men. However, 63 percent of HIV-positive MSM ages 18 to 29 were unaware of their infection, compared to 37 percent of HIV-positive MSM age 30 and older.
• Among HIV-positive MSM younger than 30, 71 percent of blacks were unaware of their infection, compared to 63 percent of Hispanics and 40 percent of whites.

“We can’t allow HIV to continue its devastating toll among gay and bisexual men, and in particular, among young black men,” said Dr. Jonathan Mermin, director of CDC’s Division of HIV/AIDS Prevention. “We need to reinvigorate our response to preventing HIV among gay and bisexual men.”

“The severity of the impact of HIV in the gay community is nothing new,” said Carl Schmid of the non-profit AIDS Institute. “What has been missing is an appropriate response by our government, at the federal, state, and local levels, and the gay community itself.”

CDC recommends that MSM be tested for HIV at least annually. Those at increased risk—men with multiple or anonymous partners, and those who use drugs during sex—should be tested every three to six months, the agency says. In the study, only 45 percent of the HIV-positive men unaware of their infection had tested in the previous year.


HIV Research Lacks Women in Trials

Cincinnati Enquirer, (09.20.2010) Peggy O'Farrell

Researchers need to find ways to make clinical trials more inclusive of women, according to Judith Feinberg, an infectious-disease expert at the University of Cincinnati. Jobs, child care, and transportation
often affect whether women complete clinical trials, which can last for a year or longer and require multiple doctor visits, Feinberg said.

Feinberg headed up the local arm of the national Gender, Race and Clinical Experience (GRACE) trial, which enrolled 287 women and 142 men at 65 centers in the United States, Canada, and Puerto Rico. The Phase IIIb clinical trial was designed to assess how well women and minorities who had failed on other HIV drugs responded to Prezista.

Women are the fastest-growing group to be newly diagnosed with HIV, so it is key that scientists learn what drugs are most effective for them. New infection rates are highest among African-American women. “The reality is we prescribe drugs to women all the time that have only or primarily been tested on men,” said Feinberg.

Of the study’s female participants, 84 percent were African-American or Hispanic. While the researchers were able to recruit the right number of women and the correct demographic mix, retaining females during the trial proved difficult.

Almost one-third of women dropped out of the 48-week study for reasons unrelated to Prezista’s side effects, compared to just one-fourth of men. The drug was equally effective in men and women, but failure rates were higher in black women because they left the trial early and thus had to be counted as treatment failures, said Feinberg.

The study’s authors concluded: “Nonsignificant, sex-based differences in responses were found during the 48-week study; however, these differences were probably due to higher discontinuation rates in women, suggesting that additional efforts are needed to retain women in clinical trials.”


**HIV Remains a Gay Disease**


“Monday is National Gay Men’s HIV Awareness Day (NGMHAD), a new addition to the growing list of CDC-sponsored efforts to draw attention to the disproportionate toll this disease takes on certain high-risk populations.

“As highlighted in the recent National HIV/AIDS Strategy, the plight of gay and bisexual men has taken a turn for the worse over the past decade. Nationally, [men who have sex with men] are 44 to 86 times more likely to be infected with HIV than their heterosexual counterparts. For whatever reason, HIV/AIDS continues to remain an undeniably ‘gay disease,’ begging the question: How have we backslid so terribly in preventing its spread?

“Today we find a new generation of gay men that never endured the fear and suffering of those who lived and died only decades before them. They never attended weekly funerals or had their social circles decimated overnight.

“In recognition of NGMHAD, following are four important, and often-overlooked, facts that all gay men should know about this disease and the new epidemic we now face.

“Newly infected individuals are both most infectious and unlikely to test positive for the virus: In a perverse twist of fortune, until newly infected people seroconvert, they will continue to falsely test negative for HIV while also being at the greatest risk of transmitting the virus to someone else.

“The advent of [post-exposure prophylaxis]. If you believe you’ve been exposed to HIV (i.e., condom breaks), go to the nearest clinic or department of health to begin PEP within three days.

“The importance of routine testing. Despite drastic changes to the CDC HIV testing guidelines in 2006, many physicians still refuse to implement such proven cost-effective approaches. Ask your primary care physician to routinely offer the test.

“Taking action against HIV: For the younger generation of gay men, it’s an accident of history that we are living in 2010, instead of 1980. If that were the case, well over half of us would be dead or dying within the next few years. We’re lucky. Conversely, if you endured those years unscathed, you know what it was like. So please share your story with the next generation of gay men. They need to hear it. And perhaps, you may motivate all of us to take action. One great way to help is by volunteering for an HIV vaccine research study at one of the many [National Institutes of Health]-sponsored sites throughout the country. Go to www.hopetakesaction.org to get involved.”

HIV treatment is costly, especially for the sickest patients

Michael Carter
Published: 27 September 2010

The average annual per patient cost of HIV treatment and care in the US was $19,912, investigators report in the online edition of AIDS. The analysis was based on 2006 figures.

Costs were highest for those with a CD4 cell count below 50 cells/mm³. This was due to the high cost of inpatient care. For patients with a CD4 cell count above this level antiretroviral therapy was the most expensive element of care.

“HIV healthcare in the United States continues to be expensive,” comment the researchers. They warn that costs are likely to increase in coming years due to the ageing of the HIV population.

Existing estimates of the costs associated with HIV treatment and care in the US date from the early years of antiretroviral therapy. In 1998, it was calculated that the annual cost of treating a patient with HIV was $18,300. Since then there have been major advances in antiretroviral therapy and HIV care and the prognosis of many patients is now excellent. Therefore earlier cost estimates are now only of historic interest.

To gain a better understanding of the costs of contemporary HIV treatment and care investigators analysed information gathered from ten large clinics across the US. Data from 2006 was analysed illustrating the costs of: inpatient care, outpatient care, emergency care, antiretroviral therapy, other drug treatment, and medical monitoring.

The patients were stratified according to their CD4 cell counts to see if costs varied according to individuals’ immune status.

The average total cost of HIV care was $19,912 per patient per year.

Costs were highest for patients with advanced disease. The cost for providing care to each patient who died was $44,000. Total annual per patient cost for an individual with a CD4 cell count below 50 cells/mm³ averaged $40,678. This compared to $16,614 for those with a CD4 cell count above 500 cells/mm³.

Antiretroviral therapy cost an average of $9360 per year for each patient with a CD4 cell count below 50 cells/mm³. This compared to average annual costs of between $11,800 and $12,313 for those with higher CD4 cell counts. Antiretroviral therapy was most expensive for those with the highest CD4 cell counts.

For patients with a CD4 cell count above 200 cells/mm³, between 61-74% of all healthcare costs were attributable to HIV therapy. However, only 23% of expenditure on the most immunosuppressed patients was for HIV medications. For these patients, inpatient care made the most costly item. Commenting on these findings, the investigators write: “people with severe immunosuppression may have extensive resistance, with few available treatment options, or may not be able to tolerate their medications”.

Costs varied according to risk group, and were lower for gay men ($18,990) than injecting drug users ($20,143). Costs also increased with age, and were only $11,854 for each patient aged under 29, compared to an average cost of $21,474 for every patient aged 50 and above.

“Overall costs of care increased as patients became more immunosuppressed”, comment the investigators. They add: “a substantial proportion of costs was attributable to antiretroviral medication. In patients with severe immunosuppression, inpatient services were the most expensive cost category.”

Of note, the estimated costs do not include those associated with mental health care, treatment for drug or alcohol abuse, or social services. Moreover, the investigators caution that the ongoing costs of HIV therapy and an increase in age-related illness means that “it is likely that the aggregate costs of HIV care will continue to increase for the foreseeable future.”

Reference
Gebo KA et al. Contemporary costs of HIV healthcare in the HAART era. AIDS 24, advance online publication, DOI: 10.1097/QAD.0b012e32835f3c14, 2010 (for free abstract and for-fee full-text click here).

Rand Paul part of AAPS doctors’ group airing unusual views

By Joseph Gerth • jgerth@courier-journal.com • September 24, 2010

Republican U.S. Senate nominee Rand Paul belongs to a conservative doctors’ group that, among other things, has expressed doubts about the connection between HIV and AIDS and suggested that President Barack Obama may have been elected because he was able to hypnotize voters.

The Association of American Physicians and Surgeons, based in Tucson, Ariz., advocates conservative and free-market solutions on health care and a variety of other political issues.
But it also uses its medical journal and Website as forums for unorthodox medical views. **Rand Paul**, a Bowling Green ophthalmologist, has touted his credentials as a doctor during this year's Senate race against Attorney General **Jack Conway**, a Democrat.

In his first television ad of the general election campaign, Rand Paul is pictured in hospital scrubs and a white lab coat.

“Preserving sight. Caring for Kentucky. Dr. Rand Paul,” the commercial says.

Speaking to the Association of American Physicians and Surgeons’ annual conference last October in Nashville, Paul said he has been a member of the group since at least 1990.

“I use a lot of AAPS literature when I talk,” he told the group.

Rand Paul’s campaign declined to answer questions about whether he supports the association’s positions. Instead, it highlighted the group’s opposition to abortion and to Democratic initiatives, including Obama’s health care law.

“Dr. Paul is member of AAPS because they believe that any health care reform should be market-oriented and embrace more freedom, not more government,” Jesse Benton, Paul’s campaign manager, said in a statement.

The AAPS was formed in 1943 as an alternative to the American Medical Association, which some conservative doctors didn’t think was protecting their rights, said its executive director, Dr. Jane Orient.

She said the group has about 2,500 dues-paying members and a total membership of about 5,000. It counts among its members Paul’s father, U.S. Rep. Ron Paul of Texas, and Rep. Paul Broun of Georgia, both Republicans. Its members are not required to be doctors.

The AMA — which is often at odds with the AAPS — had a membership last year of 228,150, said Robert Mills, media relations director for the group. He said the AMA does not comment on other medical groups.

Orient said the AAPS doesn’t generally take positions on medical issues and merely attempts to highlight views that are not widely accepted.

**Egypt’s HIV epidemic**

With only five years remaining in which to reach the Millennium Development Goals (MDGs), UN secretary-general Ban Ki-moon has called world leaders to a summit in New York from 20-22 September 2010.

The sixth MDG calls for a halt to and a beginning of the reversal of the spread of HIV by 2015 and the achievement of universal access to care, support, and treatment for all people affected by 2010. Despite global progress in placing five million people on treatment and reducing new infections by 17%, the global rate of new HIV infections continues to outstrip the expansion of treatment.

Egypt is a signatory to the Millennium Development Goals. Despite low HIV prevalence among the general population in Egypt with an estimated 10,400 people living with HIV, there is evidence of a growing epidemic among the most at risk populations and generally poor knowledge of the condition and in particular its vectors among the public. The past 20 years have marked an exponential 268 percent growth in diagnosed HIV cases in the country. In recent years, the national HIV response has made significant progress in advancing voluntary counseling and testing in 17 governorates; providing access to free antiretroviral medication for 359 people living with HIV; and supporting civil society prevention programs to the most at risk populations and people living with HIV. Total expenditure on HIV in Egypt was US$6.4 million in 2007 and US$7.7 million in 2008, 50 percent of which is contributed by the government.

In the meantime, major challenges need to be addressed to combat the advance of the epidemic and expand coverage of treatment. The advances made in the AIDS response in Egypt demonstrate that meeting the MDGs targets is feasible provided there is more focus on appropriate programs that match the epidemic situation and that sufficient resources and political commitment are in place.

In recent years, the country has been guided by emerging data from studies highlighting particular groups that are at more risk of exposure to HIV and has started focusing on programs to address prison inmates, street children, female sex workers, injecting drug users, and men who have sex with men in addition to programs for the general population.

Social stigma, which marginalizes these groups and renders them difficult to reach, is a major challenge, and causes many civil society actors avoid getting involved in such programs altogether. More focus on finding new civil society actors and building their capacity, as well as more government support to legitimize their work is needed. Additionally, cooperation between relevant government sectors is
crucial to advance HIV programs. For example it makes little sense that the police would arrest someone for holding a sterilized syringe or a condom that he/she accessed through an HIV prevention program.

There has been a paradigm shift in the field of AIDS response, where HIV is no longer addressed in isolation from other health and development issues. The eight Millennium Development Goals are not independent one from the other. Programs to prevent mother to child HIV transmission, for instance, enhance general maternal healthcare (MDG 3), while reducing child mortality (MDG 4). The role of international organizations is to support the government to capitalize on investments made in the HIV response and strengthen links across different programs. Infrastructure used for HIV prevention and testing can be further utilized to serve and monitor the spread of other diseases of national priority such as TB and hepatitis B and C in Egypt. The extensive health workforce trained for tasks related to HIV care can be utilized to serve on other health problems and generally improve the quality of care. In the same way, other MDGs compliment the effort to combat the spread of HIV.

Experience has proven that gender inequality and human rights violations are the social drivers of the epidemic. For example, progress towards MDGs 1 and 2—related to eliminating hunger, poverty reduction, and universal education reduce an individual’s vulnerability to HIV. Food insecurity can lead to coping behaviors such as selling assets, dropping out from school, migrating and engaging in commercial sex, leading to increased exposure to HIV.

Global fund raising campaigns for the AIDS response can bring in better health care for the poorest. The opportunity is that governments need to think holistically and not through vertical programs in order to maximize gains.

**Chicago churches screen parishioners for HIV**

*More than two dozen predominantly black churches participated*

After services at Southlawn United Methodist Church let out Sunday, members not only exchanged hugs and handshakes and mingled over coffee, they also waited to get their gums and cheeks swabbed.

About 40 people at Southlawn, in Chicago’s Avalon Park community, were tested Sunday for HIV during the First Ladies Health Day. More than two dozen predominantly black churches — with a combined membership of about 35,000 — offered free HIV screenings to strip away the stigma associated with the disease.

"That's really where the power of the church comes in is to say, 'Hey, you belong. You're part of us,'” said the Rev. Robert Biekman, Southlawn’s senior pastor.

Following a national trend, African-Americans in Chicago are affected in far greater numbers than other racial groups by the HIV/AIDS epidemic, according to the AIDS Foundation of Chicago. Blacks represent about 37 percent of the city’s population yet account for 56 percent of people living with HIV, according to the foundation.

Once known to have shied away from addressing the diseases plaguing their communities, many black churches have become advocates for awareness and education about HIV and AIDS.

Sunday’s event, which also included blood-pressure and diabetes screenings, was brainstormed last summer at the First Ladies Luncheon. About 100 wives of pastors from mainly black churches in the Chicago area, as well as a few female pastors, attended and decided to champion HIV testing, said Jamell Meeks, chairwoman of the luncheon and wife of the Rev. James Meeks.

"We wanted to increase the awareness in other communities and in other churches," Jamell Meeks said, adding that 75 percent of the churches that participated Sunday never before offered HIV testing.

"This seemed to be the best way to get started."

The First Ladies did just that. Several people tested positive for HIV, said Tracey Alston, a spokeswoman for the event Sunday.

Though Jermaine Bell said he uses condoms and isn’t promiscuous, he patiently waited for his screening at Southlawn. He had just gotten out of a relationship.

"You never can be too sure," Bell said.

Bell, 32, of the Chatham neighborhood, wasn’t concerned about a stigma linked to HIV, and he called on anyone who might be at risk for having the disease, such as drug users and prostitutes, to get tested.

Carl White, 22, of the South Shore neighborhood, was one of several people sitting near a closed-door room waiting for his turn to be swabbed.

"I’m not real nervous," White said, adding that he was getting tested "just to make sure that I’m being safe. That’s all."
Damon Arnold, director of the Illinois Department of Public Health, urged a handful of congregations Sunday to get tested and to seek treatment if needed.

"Your hand controls your destiny," Arnold said. "It opens the clinic door, or not."

**Gut-invading worms turn enemy T cells into friends**

Intestinal worms sidestep the immune system by inducing the development of suppressive T cells, according to a study published on September 27th in the *Journal of Experimental Medicine* ([www.jem.org](http://www.jem.org)).

Immune T cells are essential for the clearance of invading microbes, including intestinal worms, but turning off immune responses is essential for avoiding collateral tissue destruction. This job falls in part to a population of suppressive T cells called regulatory T (T reg) cells. A team of researchers, led by Rick Maizels at the University of Edinburgh, show that gut-invading worms produce a protein that generates T reg cells in mice; in this way, the worms facilitate their own survival. When this T reg–inducing pathway was blocked, the worms were expelled from the body.

T reg cells allow worms to establish a foothold in the gut, but they're not all bad news. These cells also suppress allergic responses, which may explain why humans infected with intestinal worms tend to suffer less from allergies.

**September 27, 2010**

**Computer Model Shows U.S. Vulnerable to MDR-TB Epidemic**

*Low Prevalence of TB Increases Risk for Spread of Multidrug-Resistant TB*

While the U.S. has made great progress in the prevention and treatment of tuberculosis, the nation has become more susceptible to potential epidemics of multidrug-resistant tuberculosis (MDR-TB), according a study led by Johns Hopkins researchers. Computer simulations show that as TB prevalence falls, the risk for more extensive MDR-TB increases. In addition, the simulation also showed that higher detection of TB cases without proper treatment of cases also increased risk. The study findings are published in the September 22 edition of the journal *PLoS ONE*. An interactive TB computer simulation used by the research team is available at [mdr.tbtools.org](http://mdr.tbtools.org).

MDR-TB is a form of tuberculosis that is resistant to at least two of the primary antibiotics used to treat the disease. The World Health Organization estimates that MDR-TB affects between 0.5 and 2 million people each year worldwide, but there were only 111 cases reported in the U.S. in 2006.

For the analysis, the researchers developed a computer model to simulate the potential for MDR-TB epidemics. Eighty-one scenarios covering a 500-year period were created with varying levels of treatment quality, diagnosis accuracy, microbial fitness and the degree of immunogenicity of drug-susceptible TB.

According to the study, when 75 percent of active TB cases are detected, 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 directly observed treatment 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,” said David Bishai, MD, PhD, MPH, senior author of the study and associate professor in the departments of Population, Family and Reproductive Health and International Health at the Johns Hopkins Bloomberg School of Public Health. “The most successful approach to reduce this risk for MDR-TB epidemics in the U.S. 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.”

The authors of “*Heightened Vulnerability to MDR-TB Epidemics after Controlling Drug-Susceptible TB*” include Jason D. Bishai, an undergraduate student at Stanford University and William R. Bishai, MD, PHD, professor with the Johns Hopkins School of Medicine and co-director of the Johns Hopkins Center for Tuberculosis Research.

**Zimbabwe: Nurses Steal ARVs for Backyard Pharmacies**

27 September 2010

Nurses are stealing anti-retroviral drugs (ARVs) from government hospitals to supply backyard pharmacies, a new report by the Zimbabwe Lawyers for Human Rights (ZLHR) shows.
The report titled "Corruption Burns Universal Access", also says that people with HIV and AIDS who go to government hospitals and clinics for drugs have to pay bribes to nurses in order to get the life prolonging ARVs.

Although ARVs are available in Zimbabwe there are still many reports of the difficulties patients have in accessing them. ZLHR said one of the problems for shortages could be this hoarding of drugs by government workers.

Bhekezela Maponda, a project officer who was part of the research team, said of the corrupt nurses on Monday: "What drives them is the need to get more money and if their salaries are low they engage in this corruption so as to supplement their income. You find they would have backyard pharmacies where they take drugs from clinics and hospitals to sell them so as to make more money. It was like a money spinning machine."

Nurses and other health workers in the public sector have often complained about the poor salaries, as they earn between US$150 to US$250 per month.

The ZLHR officer said the absence of a code of conduct in hospitals also meant workers could get away with the drugs scams and that staff shortages meant hospitals did not have seniors to monitor the activities of nurses and other staff.

"There is an absence of a code of conduct, but there is a patient’s charter. If there was a code of conduct, it would be easier for these cases to be looked into,” she said, adding: "The Ministry of Health commended our efforts because they do not have good monitoring and evaluation systems in place that would enable them to find this information."

Although Maponda said the Ministry of Health told them it will look into the issue, it is unlikely to be investigated as patients are afraid to come forward and testify out of fear of victimisation.

Zimbabwe’s cash-strapped health system also does not have the money to pay senior staff, who could monitor nurses.

**Phase 2 Clinical Trial to Test Interleukin-7 for Restoring CD4 Cell Count in People with HIV**

**SUMMARY:** The French biopharmaceutical company Cytheris announced last week that it has started a new Phase 2 clinical trial to test a recombinant form of the natural cytokine interleukin-7 (IL-7) as a potential therapy for increasing and maintaining CD4 T-cell counts in HIV positive people with discordant response, or poor CD4 cell recovery despite full viral suppression on antiretroviral therapy.

Below is the text of a recent Cytheris press release describing the new study.

*Cytheris Initiates INSPIRE 3, a Phase II Clinical Trial of Recombinant Human Interleukin-7 (CYT107) in Chronically Infected HIV Patients*

Study Will Assess Safety and Biological Activity of Repeated Cycles of CYT107 Administered to Restore and Maintain CD4 T-lymphocyte Counts Above 500 Cells/mcL in HIV Immune Non-Responding (INR) Patients with CD4 counts remaining between 101-350 cells/mcL after at least 2 years of Highly Active Anti-Retroviral Therapy (HAART)

Paris—September 21, 2010—Cytheris SA, a clinical stage biopharmaceutical company focused on research and development of new therapies for immune modulation, today announced that it has begun enrolling patients in INSPIRE 3, a Phase II clinical program evaluating the effect of repeated cycles of the company’s investigative immune-modulator, recombinant human Interleukin-7 (CYT107), in the treatment of chronically HIV-1 infected patients classified as Immunological Non-Responders (INR) after at least 24 months of highly active anti-retroviral therapy (HAART). The study will enroll a total of 80 patients at investigative sites in Italy, Switzerland and South Africa.

"The safety and efficacy results obtained in this trial will contribute to the clinical profile of CYT107 as a potentially important new option for HIV patients and will also serve to define the clinical end points in subsequent pivotal therapeutic studies."

"We are pleased to announce that the INSPIRE 3 clinical program is underway. The repeated treatment cycles of CYT107 in this study mimic the way the product will be used in the clinical setting and should trigger an improved and more prolonged immune reconstitution, a stabilization of patient CD4+ T cell counts above 500/mcL, and a decrease of the markers of activation/inflammation," said Michel Morre, DVM, President and CEO of Cytheris. "The safety and efficacy results obtained in this trial will contribute to the clinical profile of CYT107 as a potentially important new option for HIV patients and will also serve to define the clinical end points in subsequent pivotal therapeutic studies."
The Phase II study is designed to evaluate the safety and biological activity of CYT107 at a dose of 20 mcg/kg/week in patients with CD4+ T cell counts which have remained between 101-350 cells/mcL after at least 2 years of HAART and with plasma HIV RNA < 50 copies/mL for 18 months.

Numerous large cohort studies have shown that the health status and life expectancy of HAART-treated HIV patients able to recover and maintain their CD4+ T cell counts above 500/mcL is comparable to the healthy population. In particular these patients show a lower incidence of AIDS-related or non-AIDS-related malignancies, opportunistic infections and cardiovascular events compared to the HIV-infected population with CD4+ T cell counts below 500/mcL.

"In the INSPIRE 3 trial the goal is to establish the safety and biological activity of repeated cycles of CYT107 administered in a way that will optimize the chances that INR patients will be able to remain above 500 CD4+ T cells/mcL during the study period," said Giuseppe Tambussi, MD, Head, Experimental Therapies Unit, Infectious Disease Clinic, San Raffaele Hospital, Milan, Italy, and Principal Investigator/Study Chairman for the trial. "This is a key prerequisite for undertaking studies aimed at demonstrating the clinical efficacy of such a therapeutic regimen."

**About the INSPIRE HIV Clinical Program**

Various results from the completed INSPIRE study demonstrate the quality of CYT107-induced T cell reconstitution in Immune Non-Responding patients:

- **CYT107 administration** was clinically and biologically well tolerated.
  - 20 µg/kg/w was the dose with the best efficacy/safety ratio.
  - A single cycle (3 subcutaneous injections) induced a rapid and sustained increase of CD4+ and CD8+ T cells, with most patients treated with 20 mcg/kg of CYT107 reaching CD4+ T cells counts > 500 cells/mcL at W12.
  - All treated patients showed a very significant increase in their CD4+ T cells counts: from a baseline average at 270 CD4+/mcL patients remained at about 400 CD4+/mcL after one year of follow up.
  - CYT107 induced a brisk expansion of T cells subsets—increasing RTE, naive, central memory and effector T cells.
  - CYT107 significantly decreased markers of exhaustion (PD-1) and did not induce an increase of markers of T cell activation (HLA-DR).

Cytheris is currently conducting a repeat study, INSPIRE 2, at 20 mcg/kg/week at sites in the US and Canada. This study is designed to provide additional data for refining a PK/PD population model and to further document the ability of CYT107 to target T cells to lymph nodes and the GI tract, sites of major T cell depletion in HIV.

While INSPIRE 2 is designed to confirm the unique ability of CYT107 to trigger and support immune reconstitution in INR patients as previously documented in the first INSPIRE study, INSPIRE 3 represents the next step in the development of CYT107, testing the repeated administration of cycles of CYT107 in order to induce a long lasting immune recovery.

**About the INSPIRE 3 Study (CLI-107-14)**

INSPIRE 3 is a multicenter, open-labeled, controlled, randomized Phase II study of recombinant Interleukin-7 (CYT107) treatment to restore and maintain CD4 T-lymphocyte counts above 500 cells/mcL in HIV-infected patients with CD4 counts remaining between 101-350 cells/mcL after at least 2 years of HAART and plasma HIV RNA < 50 copies/mL for 18 months.

The primary objective of this 24-month study is to investigate the biological activity and safety of repeated cycles of CYT107 at 20 mcg/kg/week over 2 weeks, for a maximum of 4 cycles within 21 months and a maximum of 3 cycles within 12 months. The dose of 20 mcg/kg/week that will be evaluated in this study was selected based on the good safety profile and biological activity shown in two other trials, the first INSPIRE study (CLI-107-06) and the ongoing INSPIRE 2 (CLI-107-13) study, both conducted in a similar INR population. A total of 80 patients will be randomized to two arms, a CYT107 arm and control arm (HAART therapy only) with a ratio 3:1 (3 CYT107:1 control).

Secondary objectives are:

1. To further characterize long term safety in a context of repeated cycles of CYT107.
2. To characterize CYT107 Pharmacokinetics (PK) / Pharmacodynamics (PD).
3. To build a population PK/PD model of CYT107 activity.
4. To characterize the key immuno-pharmacological effects such as:
   - Increase of T cell cycling
   - Inhibition of T cell apoptosis
   - Increase of thymopoiesis and recovery of T cell repertoire diversity
   - Increase of T cell homing
5. To assess the effect of CYT107 on HIV-induced chronic systemic immune hyper-activation and its consequences.

6. To measure the time spent under prophylactic treatment for opportunistic infections.

**About Immune Non-Responders (INR)**

Approximately 25% to 30% of HIV-infected patients who receive long-term highly active antiretroviral therapy (HAART) do not exhibit a marked increase in their CD4+ T cell count, despite achieving complete suppression of HIV viral load. These patients are referred to as "immunological non-responders." Notably, the proportion of patients experiencing immunological failure depends on how failure is defined, the observation period, and the patient’s CD4+ T cell count at the start of treatment. In the longest study conducted to date, the percentage of patients with suppressed viremia who reached a CD4+ T cell count > 500 cells/ml over 6 years of treatment was only 42% for patients starting treatment at a nadir CD4+ T cell count < 200 cells/ml, and 66% for patients with a nadir of < 350 cells/ml. In a recently reported EUROSIDA cohort of 1835 patients observed for 5 years after HAART, 54.4% of patients did not reach 500 CD4+ T cell/ml after an average of 3.2 years of HAART.

**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.

Clinical trials conducted on more than 160 patients in Europe, North America and Taiwan have demonstrated a consistent safety and tolerability profile as well as the potential of IL-7 to expand and protect CD4+ and CD8+ T-cells in various pathologic conditions.

Currently, Cytheris is conducting multiple international investigations of IL-7 in HIV, HBV, HCV, idiopathic CD4 lymphocytopenia (sponsored by NIAID/NIH) and cancer, the latter including an NCI/NIH-sponsored study of IL-7 in combination with dendritic cell vaccines in a pilot study of tumor vaccination in children, and a study designed to restore CD4+ and CD8+ counts following T-cell depletion due to bone marrow or peripheral blood stem cell transplant (being conducted at the Memorial Sloan-Kettering Cancer Center in New York City).

**About Cytheris**

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. 9/28/10

**Source**

Cytheris SA. Cytheris Initiates INSPIRE 3, a Phase II Clinical Trial of Recombinant Human Interleukin-7 (CYT107) in Chronically Infected HIV Patients. Press release. September 21, 2010.

**Tesamorelin Growth Hormone-releasing Factor Reduces Visceral Fat in Diverse Patient Groups**

**SUMMARY:** Tesamorelin (TH9507, brand name Egrifta), a recombinant form of human growth hormone-releasing factor, decreased the amount of visceral abdominal fat over 1 year in a variety of sub-populations of HIV patients with lipodystrophy, according to research presented at the recent 50th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC 2010). A related study found that fat loss measured by CT scans was reflected in reduced waist size and improved patient-reported body image.

**By Liz Highleyman**

Abdominal fat accumulation, which occurs in some HIV positive people taking antiretroviral therapy (ART), is a concern both in terms of appearance and potential cardiovascular risk.

Human growth hormone reduces visceral adipose tissue (VAT), or fat deep within the abdomen, but can cause side effects including elevated blood glucose, swelling, bone pain, and carpal tunnel syndrome. Instead of administering growth hormone directly, tesamorelin stimulates the pituitary gland in the brain to secrete the hormone, which results in more steady levels and fewer side effects.
As described in the March 1, 2010 Journal of Acquired Immune Deficiency Syndromes, patients receiving tesamorelin experienced an average visceral fat reduction of about 10% at 6 months, compared with less than 1% for placebo recipients; by 12 months, the reduction in the tesamorelin arm reached 18%. These benefits were soon lost, however, when people stopped taking the drug.

Subgroup Analysis
Earlier studies included mostly white men, making it unclear how results might apply to other groups. In the present analysis, Monica Zoltowska from Theratechnologies, Inc. and colleagues looked at the efficacy and safety of tesamorelin among sub-populations based on sex, age, race/ethnicity, viral hepatitis coinfection, use of ART, and HIV viral load.

In 2 Phase 3 multicenter trials, a total of 816 HIV positive participants with excess abdominal fat (lipohypertrophy) were randomly assigned (2:1) to receive 2 mg daily tesamorelin by subcutaneous injection or placebo for 26 weeks, followed by a 26-week extension phase to assess long-term safety and duration of effects. Some patients received tesamorelin for the full 52 weeks, while others switched from tesamorelin to placebo.

Overall, patient characteristics were similar between tesamorelin and placebo recipients. Most (85%) were men, about three-quarters were white, about 20% had viral hepatitis, and the average age was about 48 years. Just over 75% had undetectable viral load.

Results
- At 26 weeks, subgroup results were consistent with the overall finding that tesamorelin reduced visceral abdominal fat significantly more than placebo.
- No statistically significant treatment-by-covariate interactions were observed.
- No important differences in adverse events or side effect profiles were seen in any subgroups throughout the 52 total weeks of treatment.

These findings led the researchers conclude that "Tesamorelin significantly reduces visceral adipose tissue in different sub-populations of HIV-infected patients with abdominal lipohypertrophy, including women, patients with hepatitis, patients with detectable viral loads, and non-Caucasians," and did so "without any clinically meaningful differences in long-term safety."

Patient-reported Outcomes
In the second study, Julian Falutz from Montreal General Hospital and colleagues investigated whether the decrease in visceral adipose tissue observed with tesamorelin correlates with anthropometric measures and patient-reported outcomes in the same 2 trials of tesamorelin versus placebo.

Results
- By week 26, decreases in VAT (about -13% vs -2%) and waist circumference were significantly greater in the tesamorelin group than in the placebo group.
- Visceral fat decreases were consistently larger in the tesamorelin arm for people whose ART regimen included a NNRTI + NRTIs, those taking protease inhibitors + NRTIs, and those taking only NRTIs.
- Treatment with tesamorelin was also associated with clinically significant improvement in patient-reported outcomes such as belly appearance distress, and patient- and physician-rated belly profile.
- The strongest correlation was seen for waist circumference, followed by patient-rated belly profile.

"Tesamorelin significantly decreases VAT in HIV positive patients with excess abdominal fat," the researchers concluded.

"Assessment of VAT using CT scan is a research technique," they noted, "but the degree to which VAT is reduced in response to tesamorelin is apparent to patients based on significant reductions in waist circumference and improvements in body image that are highly correlated with reductions in VAT."

Tesamorelin is currently under review by the U.S. Food and Drug Administration. An FDA advisory committee unanimously recommended approval in June, but the expected late July decision date came and went with no action. The agency has now indicated that it expects to make a ruling later this fall.

9/28/10
References


Facebook a Stage for AIDS Rape Documentary
Agence France Presse, (09.27.2010)

On Tuesday, filmmaker Michealene Risley will be interviewed at the Facebook Live studio in Palo Alto, Calif., just hours before her documentary on rape and AIDS myths debuts in more than 100 US theatres.

“Tapestries of Hope” spotlights the myth, common in Zimbabwe, that sex with a virgin cures HIV/AIDS. The film was inspired by the work of human rights activist Betty Makoni and the Girl Child Network in Zimbabwe.

While filming in Zimbabwe in 2007—though she had secured permission from the Ministry of Information—Risley was arrested. Risley was jailed and questioned; strangely, her interrogators’ questions focused more on life in the United States than the movie project, she said. A producer from the documentary team posted word on Facebook that Risley had been arrested.

A news reporter who had been following the documentary team on Facebook saw the news and notified a contact in the US government, who apparently helped secure Risley’s release. The team returned to the United States, and the film was finished early this year.

During the interview, Risley will field questions sent in by any of the social network’s more than 500 million members worldwide. Following the chat, she is scheduled to speak with Facebook employees.

“It’s become common for someone to find a long-lost friend, former love or missing pet on Facebook, but this is the first time we heard of Facebook getting someone released from jail,” said Marian Heath, who works on policy and safety initiatives for the company.

For more information about the documentary, visit www.freshwaterspigot.com and the “Tapestries of Hope” page on Facebook.

What next for the 2009 H1N1 influenza pandemic?
WASHINGTON, DC – September 28, 2010—Now that the H1N1 influenza pandemic is officially over, what will happen to the virus? In a perspective article published today in the online open-access journal mBio®, scientists from the National Institutes of Health delve into history and explore the fates of other pandemic influenza viruses in order to speculate on the future of the most recent pandemic virus.

“While human influenza viruses have often surprised us, available evidence leads to the hope that the current pandemic virus will continue to cause low or moderate mortality rates if it does not become extinct,” write Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases (NIAID) and his NIAID coauthors, Jeffery Taubenberger and David Morens.

The impact of the virus in the upcoming influenza season will depend directly on the degree of existing immunity in the population, provided the virus does not undergo any changes. The authors currently estimate that approximately 59% of the United States population has some level of immunity due to either exposure to the pandemic H1N1 (pH1N1) virus, vaccination or exposure to a closely related influenza virus. That number will continue to increase through immunization with the 2010-2011 seasonal influenza vaccines, which will contain the pH1N1 strain.

In order to continue to survive in a population with such a high immunity, the pH1N1 virus must undergo either an abrupt or a gradual change. In the article, the authors look at the last six influenza pandemics, going back over 163 years, and examine how those viruses adapted. While some died out for reasons not entirely understood, others, like the 1889 and 1918 pandemics, experienced an explosive recurrence. Explosive recurrence of pH1N1 is not very likely because of the already high and increasing population immunity.

“Past history and current understanding suggest cautious optimism that pH1N1 will eventually adapt to stable circulation via genetic changes resulting in continuing moderate or low mortality rates or possibly even disappear entirely,” the NIAID scientists write.

Despite their cautious optimism, the authors warn against complacency. Other post-pandemic viruses have continued to cause various rates of excess mortality among younger persons for years after the pandemic appearance and the bulk of the still susceptible population spans the under-50 age group. For
that reason they recommend infants older than six months, children, teens and young adults be aggressively targeted for seasonal influenza vaccination for not only their own protection, but to increase the overall population immunity.

**Scientists Freeze Virus Fragment in Shape Recognized by Immune System; Development Has Implications for Vaccine Design**

ScienceDaily (Sep. 27, 2010) — One approach to an HIV vaccine is to teach the immune system to recognize certain protein structures on the viral surface and produce antibodies that bind to those structures and neutralize HIV. A strategy for designing such a 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. In theory, when a fixed epitope is introduced into an animal model (or, eventually, a person), the immune system recognizes the epitope and makes antibodies against it. These antibodies could serve as an army ready to bind to the invading virus and prevent it from causing infection.

To demonstrate this scaffolding technique, the scientists applied it to a shape-changing epitope on the surface of HIV that is recognized by an HIV-neutralizing antibody known as 2F5. The epitope adopts a helical or spiral shape when removed from the surface of HIV, but the 2F5 antibody-recognizable version of this epitope has an irregular, kinked shape. The scientists placed copies of the kinked epitope into scaffolds that locked it in that form. Then the researchers injected these scaffold-bound epitopes into guinea pigs. In response, the animals’ immune systems made antibodies very similar to 2F5 that bound tightly to the epitope.

This study demonstrates that the engineering of protein scaffolds can be a potentially useful approach in vaccine design. 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.

The research is published in the *Proceedings of the National Academy of Sciences.*

**Journal Reference:**


**Immune response feeds parasite**

Posted by Jef Akst

[Entry posted at 22nd September 2010 06:00 PM GMT]

*Salmonella* is able to out compete resident gut microbes by deriving energy from the immune response that is supposed to combat the pathogen, according to a study published this week in *Nature.*

"It was a surprise," said microbiologist Samuel Miller of the University of Washington, who was not involved in the research.

"[Salmonella] is using [the host immune response] to its own advantage."

It’s an "interesting story," added Brett Finlay of the University of British Columbia, who also did not participate in the study, in an email—"a real twist on pathogenic mechanisms."

*Salmonella enterica* (specifically, serotype Typhimurium) is a gut parasite known to cause diarrhea and intestinal inflammation. The inflammatory response is part of a multipronged host immune response aimed at eliminating the bacteria, but recent studies have suggested that inflammation does just the opposite—enhances *Salmonella* growth and transmission.

A team led by microbiologist Andreas Bäumler of the University of
California, Davis, set out to determine how the bacteria might be taking advantage of the host immune response. One possibility, they thought, had to do with an unusual metabolic pathway in which *Salmonella* uses a sulfur-based molecule called tetrathionate as a terminal electron acceptor during respiration. Because few other microbes are able to use tetrathionate to respire, researchers often use the compound to identify *Salmonella* in mixed-species biological samples, such as stool from patients with diarrhea—culturing samples on tetrathionate-rich growth media increases the growth of *Salmonella* in proportion to other bacteria present. But scientists hadn’t considered this pathway to be relevant when *Salmonella* infects mammals because tetrathionate was not thought to exist in mammalian hosts.

Bäumler’s team wondered if there wasn’t actually a hidden source of tetrathionate in the gut. Mammalian intestines do, after all, harbor an abundance of thiosulphates, which result when the gut epithelial cells’ convert the toxic hydrogen sulfide released by gut bacteria breaking down sulphur-containing foods. And oxidizing thiosulphates is exactly how researchers generate the tetrathionate in the growth media used for detecting *Salmonella*. Furthermore, the inflammation process initiated by the immune system spawns reactive oxygen species (ROS), which may serve as the perfect oxidizing agents for the conversion.

Measuring the formation of tetrathionate in infected mice, the team confirmed their suspicions: They found significant levels of tetrathionate present in the intestines of infected mice, but only in those mice able to launch a normal inflammation response that would generate the ROS needed to oxidize the thiosulfates.

To confirm that it was the bacteria’s ability to use tetrathionate for respiration that allowed it to benefit from inflammation, the researchers co-cultured wild-type *Salmonella* with a mutant strain unable to perform tetrathionate respiration. While both strains performed equally well in the presence of oxygen (an alternative electron acceptor for respiration), the wild-type strain outperformed its mutant counterpart when oxygen was low or not present (as in the mammalian gut) and the thiosulfates were oxidized to tetrathionate. The results were confirmed in vivo, where the wild-type strain was markedly higher than the mutant in mouse colons 4 days after infection.

"[It’s] kind of neat trick,” Bäumler said. "*Salmonella* has these virulence factors to trigger inflammation, and this inflammation is necessary to generate tetrathionate, and tetrathionate is necessary to outgrow [the other bacteria]."

"This type of mechanism is beautiful," agreed microbiologist Wolf-Dietrich Hardt of the Institute of Microbiology in Switzerland, who was not involved in the research. "It’s exactly what we have been looking for to explain why *Salmonella* can benefit from an inflamed gut."

This is likely not the whole story, however, Hardt added. The competitive advantage demonstrated in this study for wild-type *Salmonella* over mutants unable to use tetrathionate is probably not enough to compensate for how "normally, if there’s no inflammation, *Salmonella* gets entirely outcompeted by the gut flora," he said. Furthermore, there are other bacteria that benefit from gut inflammation that do not employ tetrathionate respiration, he said. "So I would expect there’s going to be additional effects that will have to explain the real benefit for *Salmonella*."

Still, the results speak to the fantastic ingenuity of microbial pathogens, said Miller, who wrote an accompanying News & Views article in *Nature*. "Not only do pathogens evolve to resist [the host immune responses], but they’ve evolved to use them to generate more energy."


By Erica Westly

**TB or not TB?**

Bill Jacobs’s laboratory at the Albert Einstein College of Medicine in the Bronx sits in front of what was once a 500-bed tuberculosis sanitarium. For Jacobs, the now-decrepit facility serves as both a reminder of the past and a warning of what could happen if effective weapons against a wave of new drug-resistant strains of TB aren’t developed soon. “We’re basically back to where we were before drugs,” he says.

Jacobs, 54, has been in the TB field for more than 20 years. Although he started his academic career as a mathematics major, today he is known as the grandfather of tuberculosis genetics. “Before him, *Mycobacterium tuberculosis* genetics was a totally intractable problem,”
says Christopher Sassetti, a bacterial genetics researcher at the University of Massachusetts, Amherst. “Most of the work was focused on trying to understand the cell biology of the pathogen.” Today, Jacobs, a Howard Hughes Medical Institute investigator, runs one of the largest, most technologically advanced TB labs in the world.

Walking into Jacobs’s biosafety level-3 lab for the first time is a little unnerving. As we pile on item after item of safety gear—shower caps, masks, gloves, and thick plastic suits that cover even our shoes—Jacobs repeatedly assures me how safe the lab is, saying I have a better chance of contracting TB on the subway (not exactly a comforting thought for someone who regularly takes public transportation).

“We’re basically back to where we were before drugs.”

Inside the lab’s steel doors, a group of researchers shoots a training video while another conducts cell culture experiments. In the animal room, the most protected area of the lab, a one-of-a-kind apparatus that Jacobs helped design infects mice with TB through a series of pumps, then transfers the cages through the wall into a culture hood in the next room so no one has to handle them directly. The technology allows Jacobs’s staff to work with strains of extensively drug-resistant TB that most other labs in the field wouldn’t touch.

One of the most exciting discoveries to come out of Jacobs’s lab in the past few years came from a former postdoc. Rainer Kalscheuer, now at Heinrich-Heine University in Germany, was searching for genes and proteins that made some TB cells more treatment tolerant than others. After doing a microarray analysis, Kalscheuer wanted to investigate a metabolic intermediate enzyme called GlgE, but Jacobs balked. “I told him a group at Harvard had already shown that glgE was an essential gene that can’t be manipulated,” Jacobs remembers. But Kalscheuer persevered and found out that glgE could be knocked out and studied if grown in the right culture medium.

The insight would lead Kalscheuer and Jacobs in an unexpected, but fruitful, direction.

The key to creating viable glgE knockout strains turned out to be trehalose, a cell wall carbohydrate. TB bacteria that lacked glgE died instantly when trehalose was present, but survived if it was removed. The Harvard group had used medium that contained trehalose without realizing it because the carbohydrate, used as a preservative, was an unlisted ingredient.

The next step for Kalscheuer and Jacobs was figuring out the functional relationship between the two proteins. GlgE had been implicated in glycogen metabolism, but the connection with trehalose was unclear. Finally, after a painstaking series of suppressor genetics experiments, they elucidated the biochemical pathway: Glycogen and glucose produce trehalose; an enzyme known as trehalose synthase converts the trehalose into maltose; then, the maltose becomes maltose-1-phosphate, the protein that GlgE converts into glucan. When glgE is knocked out, maltose-1-phosphate accumulates, which kills the tuberculosis bacterium.

Now that Jacobs knows how glgE mutations can kill TB, he is trying to find a drug company willing to work on a project to exploit the bacterial weakness. “The GlgE gene is a great potential drug target because there’s no human homologue,” which means TB cells would be affected without harming human cells, Jacobs explains.

Back in his office, Jacobs shows me photographs from one of his first visits to South Africa where the incidence of drug-resistant TB is particularly high. All of the patients were housed together in a crowded ward, with nothing separating them from the hospital staff. “That was the only time I was ever scared of getting infected,” he recalls. Today, Jacobs has several collaborators in South Africa and is helping to build a state-of-the-art TB research facility there. The goal is to get more African researchers using the latest diagnostic technologies, but equally important, Jacobs says, is encouraging new drug development. “One drug is not enough,” he says. “Our collaborators in Africa say they need at least three new TB drugs.”

Correction (September 10): The original version of this article mistakenly identified trehalose as a protein. It is a carbohydrate. The Scientist regrets the error.

comment: Face reality
by Anita Allen, [Comment posted 2010-09-25 03:09:41]

When is the scientific community going to acknowledge that vaccinating TB naive babies with BCG is the cause of rampant TB infection? In one province of South Africa with 87% BCG coverage, 41% of the population has TB. The fact is WHO considers BCG as 100% contra-indicated in immune compromised (defined as HIV positive) babies. In poverty stricken regions the majority of babies suffer from malnutrition and will be immune compromised without the need for a putative virus cause. The untitled assumption that it is unethical not to give BCG to babies, should be put to rigorous test before another babies gets the BCG.

comment: Could the World Community Grid be of Assistance ?
by anonymous poster, [Comment posted 2010-09-24 21:11:01]
Has Dr Jacobs considered putting together a proposal, or collaborating with others to put together a proposal, that could be run for free as a non profit project by the 500,000 + members of the World Community Grid coordinated by IBM?

Our PC computers could be used to screen vast numbers of substances as potential drug candidates against multi-drug resistant TB. We already work on projects dealing with multi-drug resistant HIV and results to date seem promising. We have also helped screen drug candidates against Dengue Fever, and Influenza. Collectively the World Community Grid forms one of the 5 most powerful supercomputers in the world and works for free on non-profit humanitarian projects.

Relevant URL’s are provided below.

**LINK**

**comment:**

**Trehalosa as an inhibitor drug**

by MARTIN ERNESTO TIZNADO HERNANDEZ, [Comment posted 2010-09-24 12:37:27]

It will easy to use trehalose as a drug against TB, as well as safe....

**comment:**

**maltose-1-phosphate not a protein**

by HILLEL BRANDES, [Comment posted 2010-09-16 08:24:03]

Neither is maltose-1-phosphate “the protein that GlgE converts to glucan.”

**comment:**

**Clarification: “Trehalose” is not a protein**

by Andrew Robertson, [Comment posted 2010-09-10 13:15:04]

The article makes two or three references to trehalose as a protein. Trehalose is not a protein, it is a carbohydrate.

By Cristina Luiggi

**The Discovery of Penicillin, circa 1928**

It was the wonder drug of the 20th century: A yellow liquid that seeps from the spores of the *Penicillium* fungal mold and contains a compound that shatters the cell walls of bacteria responsible for common diseases such as pneumonia, strep throat, scarlet fever, syphilis, and meningitis. With steep reductions in human mortality rates and drastic improvements in quality of life, penicillin may very well be one of mankind’s greatest discoveries.

© True Comics

Scottish doctor Alexander Fleming observed the mold killing his *Staphylococcus* cultures in late 1928 while working at St. Mary’s Hospital in London. But by the start of World War II, no one had figured out how to efficiently extract the active ingredient from *Penicillium*, whose concentration “is almost the same as gold in sea water,” says Robert Bud, Principal Curator of Medicine at The Science Museum in London and author of *Penicillin: Triumph and Tragedy*.

It wasn’t until the end of 1940 that doctors at Oxford University had collected enough penicillin to treat one person: a policeman who got blood poisoning from a small scratch on his face. Unfortunately, his intravenous treatment of penicillin used up the entire stock of the drug. Doctors tried recycling penicillin from his urine to continue his treatment, Bud says, but with barely one hundredth of a gram of antibiotic per gallon of urine, it simply wasn’t enough. The man died shortly after the penicillin ran out.
In 1942, the Russians held the record for treating the most patients with the drug, Bud says, scraping the *Penicillium* off the walls of damp air raid shelters and rubbing the fungal juice directly onto affected areas. Two years later, researchers finally succeeded in mass-producing the antibiotic by growing a mutant *Penicillium* strain in corn starch liquor in large metal tanks—just in time to aid the thousands of soldiers who would be wounded on the beaches of Normandy on D-Day.

The wonder drug has lost some of its killer properties in the decades following its initial widespread use, with hospitals reporting penicillin-resistant infections as early as the mid-1940s. A new antibiotic called methicillin initially served as a good alternative, but bacteria have since evolved ways to circumvent methicillin’s deadly grip as well. Methicillin-resistant *Staphylococcus aureus* (MRSA) was responsible for around 20,000 deaths in the United States in 2005.

**Comment:**

*Discovery of Penicillin 1928? Maybe*

by anonymous poster, [Comment posted 2010-09-29 01:49:52]

Before the Europeans invaded the American continent the indians of Mexico had antibiotics based in fungi growth in bolls of corn mass. Pieces of those bolls were eaten and had effects on infections.

**Comment:**

*Mythology*

by anonymous poster, [Comment posted 2010-09-28 17:06:52]

Oh the British mythology of Fleming continues.

**Comment:**

*Remember Norman Heatley*

by Paul Browne, [Comment posted 2010-09-28 07:00:47]

I have to agree with earlier comments, Fleming was a great scientist, but was also something of a self-publicist who was lucky on several occasions. This didn’t only apply to his discovery of penicillin, he was very fortunate that the first patient he treated didn’t suffer serious neurological side effects as a consequence.

**LINK**

Florey, Chain, and Heatley should get more credit for their role in developing Penicillin, a role that depended less on luck than on sheer hard graft and innovative science. In particular it is a shame that the Nobel Prize can only be awarded to 3 individuals in one year, as Norman Heatley really did deserve to receive it for his ingenuity in overcoming many of the problems in purifying penicillin.

**Comment:**

*Who discovered the action of penicillin?*

by STEPHEN BARNES, [Comment posted 2010-09-27 17:06:19]

This article overly simplifies the origins of the discovery of penicillin. Some think that the first systematic discoverer of penicillin was a Frenchman, Eric Duchesne. He submitted a thesis in 1896 about the effects of a green mould on bacterial growth. J. W. Henderson has written an article in the Mayo Clinic Proceedings (72: 683-687, 1997) on the history of the discovery of penicillin that puts
Fleming’s role into perspective. However, it’s possible that the real discoverers of the effect of penicillin mould on bacterial growth are much more ancient than even Duchesne. Many non-Western societies have long been aware of the value of plants and microorganisms for use as medicines.

**comment:**

**The mold in Dr. Florey's Coat**
by KEITH SEIFERT, [Comment posted 2010-09-27 14:42:59]

There are lots of stories, and many of them are in the book by Eric Lax, The Mold in Dr. Florey's Coat. Definitely worth a read.

**comment:**

**Myopia**
by Mark Cannell, [Comment posted 2010-09-27 14:37:16]

Yikes, even Wikipedia has a better account than this. Apart form Chain and Florey, let’s not forget Norman Heatley.

**comment:**

**Peter Bradley**
by Peter Bradles, [Comment posted 2010-09-27 12:43:22]

Is this a case of British revisionist history? Fleming (the Brit) glorified for a chance observation and the people who did the hard work—Floey and Chain consigned to the dustbin of history.

**comment:**

**So what?**
by Miguel Vicente, [Comment posted 2010-09-27 12:12:05]

Is this all that there is to this post? It seems a rather incomplete and superficial account of well known facts. Which is the purpose of the comics?

**comment:**

**Skimming Over Penicillin Detail**
by Brendon Coventry, [Comment posted 2010-09-24 19:37:03]

The article skims over the fact that Fleming did not go on to do anything with his finding, in fact, it was left to Howard Florey and Ernst Chain (non-British) many years later to realise what it meant and to develop the chance finding into a true discovery. This was not supported by the British Government and funding was so poor that the project nearly folded several times, were it not for Florey’s unyielding tenacity, and finally an American philanthropic group donated $200 to permit development to proceed to the point where it could prosper. The war effort finally brought funds that moved this on further, and the rest is history. I note the real heroes Florey and Chain are not mentioned in this little article—nor their unyielding quest for scientific discovery and clinical success—an all too often omission in records of discoveries! Without these people Penicillin would never have been then, for the war effort, and possibly to date? These points are all well recorded in history—if you look!

**Institute of Medicine Recommends Changes for People with HIV/AIDS to Qualify for Disability**


The Institute of Medicine (IOM) recently provided guidance to the Social Security Administration on updating its Listings of Impairments—a tool that helps SSA quickly assess whether someone with HIV or another condition qualifies for benefits. The HIV/AIDS listings were last updated in 1993.

The following are the new recommendations to qualify someone as eligible for SSA disability payments:

- A CD4 cell count at or below 50 cells per microliter of blood. “Because CD4 counts can change in response to antiretroviral therapy, claimants allowed disability in this way should be regularly reevaluated,” IOM’s report states.
- Several rare but fatal or severely disabling HIV-associated conditions, including dementia and certain types of AIDS-related cancers. Benefits for these diseases should be permanent, IOM said.
- Severe HIV-associated conditions such as hepatitis or heart disease, which are already covered by another section of SSA’s full listing. These claimants should be regularly reevaluated, according to IOM.
- HIV-associated conditions such as wasting syndrome that are not included in another section of the listing. These conditions must be severe and limit function. “Claimants allowed in this way should be regularly reevaluated,” IOM suggested.

The biggest change would be that HIV-positive applicants seeking disability would have to reapply to SSA every three years. That policy pertains only to new applicants, not to those already receiving disability through SSA.

Raeline Nobles, executive director of the Dallas-based non-profit AIDS Arms, said SSA currently allows disability for people with a CD4 count of 200. She said she sees many clients who get along fine with a CD4 count of 100. “But politically, it might be a way to cut some expensive corners,” she said, adding, “50 seems awfully low to me.”

Examing Future Adolescent Human Papillomavirus Vaccine Uptake, With and Without a School Mandate

*Journal of Adolescent Health Vol. 47; No. 3: P. 242-248.e6*, (09. .2010) Amanda F. Dempsey, MD, PhD, MPH; David Mendez, PhD

The aim of the current study was to “develop a model of adolescent human papillomavirus vaccine utilization that explored future HPV vaccination rates, with and without a school mandate, for the vaccine at middle school entry.”

The investigators developed a dynamic, population-based, compartmental model that estimated HPV vaccine uptake among US female adolescents over a 50-year time horizon. Data on parental attitudes about HPV vaccine and adolescent health care utilization levels were included.

Without a mandate, the investigators’ model predicted that 70 percent coverage, a lower threshold value used in many prior modeling studies of HPV vaccination, would not be achieved until a mean of 23 years after vaccine availability. Maximal coverage of 79 percent was achieved after 50 years. With a school mandate in effect, utilization increased substantially, with 70 percent vaccination coverage achieved by year eight and maximal vaccination coverage, 90 percent, achieved by year 43.

“Our results suggest that vaccine utilization is likely to be low for several years, though strong school mandates might improve HPV vaccine uptake. These results affect the interpretation of previous modeling studies that estimated the potential clinical effects of HPV vaccination under assumptions of very high vaccine utilization rates,” the investigators concluded.

Sergeant’s Case a Cautionary Tale of STDs

*Wichita Eagle*, (09.23.2010) Deb Gruver

“Sedgwick County’s health department is using the case of an Air Force sergeant accused of having unprotected sex without disclosing his HIV-positive status as a teachable moment. And a warning.

“Almost all the county’s syphilis cases can be traced back to anonymous sexual encounters that began online, health department Director Claudia Blackburn told Sedgwick County commissioners Wednesday.

“[The sergeant], stationed and now confined at McConnell Air Force Base, has been charged in military court with aggravated assault, adultery, obstructing justice, and other offenses, accused of knowingly having unprotected sex with others without telling them he is HIV-positive.

“Documents say [the sergeant] used adult websites to find casual sex partners and attended ‘swinger’ parties where promiscuous sex is common. ...”

“The executive director of Positive Directions, a Wichita non-profit that provides services to people with HIV and AIDS, noted this week that while people may not relate to swinger parties, some might put themselves at risk by having one-night stands at bars.

“Blackburn said 729 people in the county are living with HIV or AIDS. The county recorded 33 new HIV cases last year, up from 13 in 2000. Last year, the county also recorded: 703 new cases of gonorrhea; 2,605 new cases of chlamydia; 32 new cases of syphilis.

“Interviews with clients have shown that two risk factors are associated with most syphilis cases reported in Sedgwick County, Blackburn said.

“Those risk factors are using the Internet and other forms of technology to solicit sex partners, and ‘frequency and speed of travel.’ Blackburn said one case involved 90 sex partners, 77 percent of whom were out of state, exposed to the disease while the patient was on vacation or business trips.

“Anyone with questions about testing may call the department at 316-660-7300. Because the department is trying to track potential cases related to the charges against [the sergeant], Blackburn said people are asked to mention the McConnell case if applicable.”

Mass rape and HIV in conflict-affected countries: despite relatively low incidence, researchers stress urgency of interventions for thousands of women in need

Kelly Safreed-Harmon
Published: 30 September 2010

Mass rape during armed conflict may account for several thousand new cases of HIV per year in sub-Saharan Africa, according to an article in the Journal AIDS.

Researchers drew this conclusion after analysing data from seven conflict-affected countries with high HIV prevalence: Burundi, Democratic Republic of Congo (DRC), Rwanda, Sierra Leone, Somalia, Sudan and Uganda.
According to their calculations, annual HIV incidence due to mass rape may range from four cases per 100,000 women and girls in Somalia to 20 cases per 100,000 women and girls in Uganda, the countries with the lowest and highest HIV prevalence, respectively, among the seven countries.

The countries with the most estimated mass rape-associated HIV infections per year were DRC, with a total of 1120 (median) (interquartile range [IQR], 527 – 2360), and Uganda, with a total of 2172 (median) (IQR, 1031 – 4668). The sum of the estimated number of infections for all seven countries was 4948 (median) (IQR, 2043 – 10,329).

Data limitations make it difficult to arrive at highly specific estimates regarding HIV transmission in conflict settings.

Variables that figure into such estimates include the proportion of women and girls who are raped, the proportion of assailants who have HIV and the probability of HIV transmission occurring with each act of rape.

The authors of the article, like other researchers examining this issue, needed to build their analysis on a complex series of assumptions.

Guided by what has been documented about rape in conflict settings, the authors allowed for the possibility that 1% to 15% of women and girls could be raped. Their assumptions about the lowest and highest HIV prevalence likely to be found among assailants took into account widespread indications that military forces in countries with large-scale HIV epidemics have higher-than-average HIV prevalence.

The authors drew on other literature to set the average probability of transmission per act of rape at 0.0028 to 0.032. (In Africa, the per-act probability of HIV being transmitted from an infected to an uninfected person during consensual heterosexual sex in the absence of sexually transmitted infections is estimated to be 0.0009.)

Although any range of estimates based on such broad parameters will itself be broad, the study findings still provide compelling evidence of the large-scale HIV prevention and treatment implications of conflict-associated rape.

Furthermore, mathematical modeling efforts to date, including this one, have not reflected indirect pathways by which rape may increase the number of HIV infections in a conflict-affected community. As the authors note, “Mass rape also indirectly increases HIV incidence through at least two other mechanisms: women who become infected through rape can transmit HIV to their future male partners and some survivors of rape may be infected with [another sexually transmitted infection] that increases their susceptibility to HIV.”

The authors also point out that rape survivors who become HIV-positive and pregnant are at risk of mother-to-child transmission of HIV.

 Until recently it was speculated that mass rape in conflict-affected countries with large HIV epidemics might be helping to drive up or maintain overall national HIV prevalence levels. Key studies published in 2007 and 2008 showed that the available data did not support this hypothesis. Nonetheless, the sheer number of HIV cases thought to be attributable to mass rape calls attention to the need for HIV prevention and treatment programming as part of the response to conflict-related humanitarian crises.

*Guidelines for addressing HIV in humanitarian settings*, a recent publication by a United Nations-convened task force, recommends offering post-exposure prophylaxis (PEP) to rape survivors whose assailants may have exposed them to HIV.

However, the antiretrovirals used in PEP regimens may not be widely available in conflict settings. Even if they are, delays in accessing medical treatment may prevent rape survivors from benefitting from PEP, since it must be initiated within 72 hours of an episode of possible exposure to HIV.

The authors of the recent study echo the authors of the 2008 study that failed to find a link between mass rape and HIV prevalence by emphasising the importance of providing all rape survivors with appropriate medical and psychosocial services, including HIV-related services.

The group of researchers who published in 2008 stated, “Our findings must not be interpreted to say that widespread rape in conflict-affected countries does not pose a serious problem to women’s acquisition of HIV on an individual basis or in specific settings. Although the increase in total prevalence is small compared with the overall population, it is horrific that tens of thousands of women acquire HIV from sexual violence during conflict.”

Meeting the HIV-related needs of rape survivors requires considerably more than providing access to PEP. Other relevant services include those relating to voluntary counseling and testing; prevention of mother-to-child transmission of HIV; and antiretroviral treatment.
References

Arbitrary Arrests of Gay Men in China Violate Human Rights, Undermine Effective HIV Prevention and Treatment
Article Date: 30 Sep, 2010
September 30, 2010 (Oakland, California)–The Global Forum on MSM & HIV (MSMGF) stands with the China HIV/AIDS CBO Network in strongly condemning the arbitrary arrest and mistreatment of more than 80 gay men at a popular Beijing park on Sunday night. According to local activists, 20 police vehicles descended on the park and rounded up dozens of men, forcing them to be photographed, fingerprinted, and undergo blood testing at the local police station. Such discriminatory actions are not only grievous violations of human rights, they also work to seriously undermine efforts to effectively prevent and treat HIV among men who have sex with men (MSM).

Singling out sexual minorities for arrest and documentation sabotages efforts to control HIV by perpetuating an environment of fear and mistrust that inhibits open discussion and service-seeking behavior. In such hostile conditions, revealing one’s sexual behavior and risk factors becomes a liability, driving many MSM outside the healthcare system. Experiences of discrimination have also been linked to increases in high risk sexual behavior among MSM.

Reports of forced blood tests are especially disturbing. Forced testing is a violation of internationally recognized rights to security of person and to privacy. Gay men and other MSM must have access to high-quality health services that provide for their specific needs. The government should invest in friendly and competent services that MSM will actually want to visit, rather than conduct forced testing in an environment without any guarantee of counseling, referral, or confidentiality.

In China, MSM are 45 times more likely to be infected with HIV than the general population, and they accounted for roughly one third of new infections in 2007. While homosexuality was decriminalized in China in 1997, authorities have continued to clamp down on non-governmental organizations, public gatherings and artistic events geared toward the gay and lesbian community.

“This is an unfortunate reminder that decriminalization of homosexuality is only the first step on the road to human dignity and effective health services for sexual minorities,” said Dr. George Ayala, Executive Officer of the MSMGF. “Legal protection from discrimination and abuse is essential to ensuring the health and well being of most at risk populations.”

These events represent a major step backwards in China’s response to its domestic epidemic. Incidents like this run the risk of squandering the notable progress China has already made toward addressing HIV among sexual minorities. If authorities do not put a stop to these kinds of abuses, the country will miss a significant opportunity to model a more forward-looking, evidence-based and ultimately effective approach to this deadly pandemic.

Did Doctors Jumpstart the HIV Pandemic?
Reuters Health, (09.23.2010) Frederik Joelving
Two new studies suggest a health care link as HIV evolved from a chimp’s infection, possibly transmitted to bush meat hunters by bite or blood, to its earliest human dissemination and global spread.

Scientists have theorized that the HIV pandemic was sparked after colonial-era urbanization fueled changes in sexual behavior. The new studies by Dr. Jacques Pepin, of the Université de Sherbrooke in Montreal, and colleagues propose that sexual transmission might have been secondary to initial blood-borne dissemination of HIV from a few isolated cases. Syringe reuse during early 20th century mass-vaccination campaigns against endemic diseases in Equatorial Africa may have inadvertently spread HIV and jumpstarted the pandemic, they suggest.

“What happened is that for a long time, the needles and syringes used to administer the intravenous drugs were not single-use,” Pepin said. “There were a lot of patients and not a lot of needles, so the sterilization of needles was not very efficient.”

“If HIV was present in one of these patients 50 years ago, we can assume that they probably transmitted HIV,” Pepin said.
Because villagers from that era with HIV would be long dead, Pepin used less-lethal viruses, hepatitis C virus (HCV) and human T cell lymphotropic virus 1 (HTLV-1), to track the colonial-era vaccination campaigns among villagers.

In the Central African Republic, the only risk factor for HCV genotype 4 infection was having received injections for sleeping sickness before 1951, the cross-sectional study found. HTLV-1 infection was associated with having two or more such injections (adjusted odds ratio [AOR], 2.03; 95 percent confidence interval [CI], 1.01-4.06) and with transfusions (AOR 2.82; 95 percent CI, 1.04-7.67). The number of people age 65-plus who had been treated for sleeping sickness was six times lower than what would be expected from historical data—possibly because many patients were lost to AIDS, Pepin explained.

In Cameroon, 56 percent of participants were HCV-positive. Independent risk factors included IV treatment against malaria, older age, attendance at an ethnic school (women only), and traditional male circumcision.

The studies, “Risk Factors for Hepatitis C Virus Transmission in Colonial Cameroon” and “Iatrogenic Transmission of Human T Cell Lymphotropic Virus Type 1 and Hepatitis C Through Parenteral Treatment and Chemoprophylaxis of Sleeping Sickness in Colonial Equatorial Africa,” were published in Clinical Infectious Diseases (2010;(51):768-776 and 777-784).

World Bank President Calls For New, More Open Approach To Economic Development

"World Bank President Robert Zoellick on Wednesday called on economists to rethink the way they look at issues affecting developing nations and said he was overhauling the way his institution approached research," Reuters reports (Wroughton, 9/29).

At a speech at Georgetown University ahead of next week's World Bank and IMF meetings, "Zoellick said development economics was in need of 'rethinking' as the experiences of nations such as China and India become more relevant to other nations seeking economic and social progress," the Financial Times reports.

"A new multipolar economy requires multipolar knowledge," he said. "We need to democratise and demystify development economics, recognising that we do not have a monopoly on the answers," Zoellick said, adding that economists in developed nations should not focus on one model for development and should be more open to "differentiated policy approaches."

"The right policies may differ across phases of development," he said, highlighting the debate over promoting export-led growth versus domestic demand, the approach to innovation and financial regulation. 'What may safeguard in one context may strangle in another,' he said," according to the Financial Times (Politi, 9/29). Though the global economic downturn played a role in Zoellick's call for a new approach to development economics, he said the problem pre-dates the poor economy, Reuters writes. "Even before the crisis there was a questioning of prevailing paradigms and a sense that development economics needed rethinking," he said. "The crisis has only made that more compelling" (9/29).

"The flow of knowledge is no longer North to South, West to East, rich to poor. Rising economies bring new approaches and solutions," Zoellick said. He "noted that emerging economies are now key variables in the global growth equation, and the developing world is becoming a driver of the global economy," Xinhua writes (9/29).

In the speech, Zoellick "said the World Bank would apply its economic know-how to studying issues from food security to what drives growth to be more relevant to the developing countries it assists," Reuters reports.

"He identified four areas that needed more research. These included a better understanding of how economic transformations occur and why some countries are able to grow and others remain trapped in dire poverty. ... Zoellick said research should look closer at risk to do with natural disasters to health pandemics, and climate changes that are affecting food production. Lastly, more study was needed to gather evidence and data to evaluate and assess the effectiveness of development efforts, including aid, he added," the news service reports (9/29). The knowledge gaps, identified in the speech, were outlined in a World Bank paper published on Wednesday, according to a World Bank press release (9/29).

"Zoellick also focused on increasing the transparency of the Bank and making its data more available to outside scholars and policymakers," Inter Press Service reports.

"He said the Bank is working to make its research and models more available and user-friendly and regretted that in years past some data was only available by purchase. This would allow 'researchers civil
society and local communities to come up with their own findings and double-check ours,' he said" (Berger, 9/29). "No longer can the model solely be to research a specific issue and write a paper hoping someone will read it," said Zoellick, the Wall Street Journal writes. "The new model must be ‘wholesale’ and networked," Zoellick said.

Some economists reacted favorably to Zoellick’s remarks. The comments are "generally not only in the right direction, but very useful," Nobel Prize-winning economist Michael Spence said of the speech. "The speech hits all the right notes: the need for economists to demonstrate humility, eschew blueprints ... and focus on evaluation but not at the expense of the big questions," said Harvard economist Dani Rodrik, "who favors a stronger government hand in development," the newspaper writes.

"But the reaction wasn’t unanimous," the Wall Street Journal notes, quoting New York University’s William Easterly, "a former World Bank economist who is skeptical about the value of foreign aid." Easterly described the speech as "amazingly presumptuous" and said the current approach to economic research, where economists critique each other’s ideas, works well. Easterly said World Bank economists are often pressured by their bosses "to reach the 'right' conclusions," which is that foreign aid works and that World Bank loans are helpful.

However, Martin Ravallion, the bank’s head of research, responded, "I have never been told what conclusions I should reach, and I doubt very much that anyone told Bill Easterly what conclusions he should reach in his many years working for the Bank’s research department" (Davis, 9/30).

Dengue-Blocking Mosquitoes Approved For Release In Northern Australia
It was is being described as a “world first,” mosquitoes "infected with a bacteria known to block transmission of dengue fever have been approved for release into the wild in Australia’s north," the Herald Sun reports. The Eliminate Dengue Project "has received final regulatory and safety approvals" and plans are underway to begin field trials "early next year." Project leader Scott O’Neill said, "If it works it could be a sustainable low-cost approach to dengue control which will be much better, we think, and more environmentally friendly than spraying lots of insecticides into the environment to kill the mosquitoes" (9/30).

Oral Visceral Leishmaniasis Treatment Receives Orphan Drug Status
iCo Therapeutics Inc. said Wednesday that its oral program iCoB009 for the treatment of visceral leishmaniasis received Orphan Drug status from the FDA, RTTNews reports. The drug is an oral formulation of Amphotericin B, which is currently only available in intravenous formulations. "With the grant of Orphan Drug status for its product, the company can avail state assistance, including waiver of certain taxes and application-filing fees, study design support, grant funding for clinical trials and seven years of marketing exclusivity after the approval of the drug," according to the news service (9/29).

Researchers sequence genome of mosquito that spreads West Nile virus
UC Riverside researchers spearheaded the multiyear project that could result in novel strategies to fight West Nile and other Culex-transmitted diseases
RIVERSIDE, Calif. – Last year, 720 people in the United States became infected with West Nile virus, a potentially serious illness that is spread through the bite of a mosquito – the Culex mosquito – that has first fed on infected birds. Such mosquitoes have the virus eventually located in their salivary glands and transmit the disease to humans and animals when they bite to draw blood.

To understand the genetic makeup of the Culex mosquito, and how the insect is able to transmit this and other viruses, an international team of scientists, led by geneticists at the University of California, Riverside, has sequenced the genome of Culex quinquefasciatus, a representative of the Culex genus (or group) of mosquitoes.

A close study of the genome, the researchers say, could give scientists the clues they need to target specific Culex genes that are involved in the transmission of West Nile virus, St. Louis encephalitis, lymphatic filariasis and other diseases spread by the Culex group of mosquitoes.
mosquitoes. Knowledge of such genes would be an important step in developing strategies to combat the spread of these pathogens.

The genomes of Anopheles gambiae (which transmits malaria) and Aedes aegypti (which transmits yellow fever and dengue) were published in 2002 and 2007, respectively. Now, with the sequencing of Culex quinquefasciatus, scientists have completed the triangulation of entire genome sequences of three genera of mosquitoes that are the main vectors of deadly human diseases, and will have access to representative genomes from the three mosquito groups.

"We can now compare and contrast all three mosquito genomes, and identify not only their common genes but also what is unique to each mosquito," said Peter Arensburger, an assistant research entomologist in the Center for Disease Vector Research and the Department of Entomology, who led the substantial bioinformatics component of the multiyear research effort. "Moreover, now that we have sequenced the Culex genome, we can begin to identify which mosquito genes get turned on or turned off in response to infection – knowledge that is critical to developing strategies for preventing the transmission of West Nile virus and other disease vectors."

Study results appear in the Oct. 1 issue of Science.

The researchers report that Culex quinquefasciatus, also known as the southern house mosquito, has a genome size of 579 million nucleotides, which is intermediate between the genome sizes of Anopheles gambiae (278 million nucleotides) and Aedes aegypti (about 1380 million nucleotides). However, Culex quinquefasciatus has a higher number of genes (18,883 genes) than Anopheles gambiae (12,457 genes) or Aedes aegypti (15,419 genes).

"We do not know why this is the case," said Arensburger. "Culex quinquefasciatus is very widely distributed throughout the globe; the same species is found in California and South Africa. It is possible that the large number of genes in this mosquito helped it survive in a wide variety of habitats."

The researchers also report that the genome for Culex quinquefasciatus bears more similarity to the Aedes aegypti genome than the Anopheles gambiae genome.

Thirty-seven institutions collaborated with UC Riverside on the research project that began in 2004. Besides Arensburger, the UCR team includes Peter Atkinson, the director of the Center for Disease Vector Research and a professor of entomology, and Alexander Raikhel, a distinguished professor of entomology.

"We coordinated with researchers around the world to accomplish the sequencing of the Culex genome," said Atkinson, the senior author of the study and the principal investigator of the grants that funded UCR's contribution to the research. "We could not have done this without the outstanding computing support we received from UCR's Institute for Integrative Genome Biology. It enabled us to perform vast and complex analyses here on campus, and gave us the confidence to get the project going and completed."

With more than 1,200 described species, Culex is the most diverse and geographically widespread of the three mosquito genera. The adult mosquito measures 4-10 millimeters. Only females spread disease. Culex-transmitted diseases, such as West Nile virus, are difficult to eradicate because birds and animals the mosquito feeds on are mobile, capable of spreading disease quickly over large areas.

West Nile virus first appeared in the United States in the summer of 1999. Since then it has been found in all 48 contiguous states. The research paper in Science is accompanied by a second paper, led by researchers at Boston College, Mass., and Iowa State University, that focuses on a set of immune genes in Culex quinquefasciatus. The paper explores why some of these genes are "upregulated" (show an increase in gene expression) while others are "downregulated" in response to pathogens. Arensburger, Atkinson and Raikhel are coauthors on the companion paper in the same issue of Science on Culex immunobiology with Raikhel's laboratory contributing significantly to this work.

With the sequencing of the Culex quinquefasciatus genome completed, UCR researchers will focus next on genes of particular interest to efforts aimed at preventing the spread of human diseases by these mosquitoes.

**Scientists reveal important clues to how bacteria and viruses are identified as enemies**

New research published in the Journal of Leukocyte Biology suggests complement system activation is initiated by receptors on the inside and outside of immune cells using unique and shared pathways.
A new research report in the October 2010 print issue of the Journal of Leukocyte Biology (http://www.jleukbio.org) sheds important light on how our immune systems detect invading organisms to be destroyed and removed from our bodies. The information from this research should ultimately help lead to the development of new drugs and treatments that allow health care providers to prevent runaway immune reactions that can have devastating consequences for people.

“Our study helps us to understand exactly how the immune system is activated when it comes across infection from bacteria or viruses,” said Melanie J. Scott, M.D., Ph.D., an author of the research report from the Department of Surgery at the University of Pittsburgh, Pennsylvania. “The more information we have about how this process works, the more likely we are to be able to help our immune systems fight off attacks from infections.”

To make this discovery, scientists examined the production of a specific part of the complement system (called “factor B”) in macrophages, an immune cell that both attacks foreign invaders and marks them for death by other types of immune cells. The researchers wanted to know if a molecule found on the outside of bacteria (lipopolysaccharide) or a synthetic version of a molecule found in some viruses (polyI:C) would stimulate factor B production by macrophages. The levels of factor B produced inside the cell were measured, as was the amount released from the cell. Results showed that lipopolysaccharide used a specific receptor on the outside of cells (TLR4) to produce factor B. polyI:C also stimulated factor B production in macrophages, not through its specific cell surface receptor (TLR3) but through another receptor that is located within cells. This shows that bacteria and viruses can produce similar end results in activating the body’s defense systems, but they use different pathways to do the activation.

“As this research shows, the immune system is incredibly complex. It also highlights the redundancy which is vital to our survival,” said John Wherry, Ph.D., Deputy Editor of the Journal of Leukocyte Biology. “Viruses and bacterial have evolved many strategies to avoid immune responses, but the immune system counters with additional tricks and alternative pathways. This research helps us better understand one very important set of redundant pathways that regulates a key defense mechanism and identifies therapeutic targets for controlling that response.”

**Statement: Study finds genital herpes vaccine ineffective in women**

An experimental vaccine intended to prevent genital herpes disease in women, although generally safe and well-tolerated, proved ineffective when tested in the recently concluded clinical study known as the Herpevac Trial for Women.

The Phase 3 trial, sponsored by GlaxoSmithKline (GSK) Biologicals, based in Belgium, with support from the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, began in 2002. A total of 8,323 women aged 18–30 years participated in the trial at 50 sites in the United States and Canada. At the time of their enrollment, the study participants were free of the two types of herpes simplex viruses (HSV), HSV-1 and HSV-2.

Participants in the Herpevac trial were randomly divided into two groups. One group received the candidate vaccine, containing HSV protein along with an adjuvant intended to boost immune responses. The second, control group received a version of Havrix, a licensed vaccine against hepatitis A. This study design gave all participants the potential opportunity to be protected against either genital herpes or hepatitis A. GSK developed the candidate vaccine and also manufactures Havrix.

Each volunteer was vaccinated at the beginning of the study and again one and six months later. The participants were followed for 20 months after the initial injection and evaluated at each visit for HSV infection and genital herpes disease.

In two earlier studies involving men and women who did not have genital herpes but whose sexual partners were known to be infected, the candidate vaccine prevented genital herpes disease in more than 70 percent of the female volunteers who were free of HSV-1 and HSV-2 but had no clear effect in men. These studies formed the basis to conduct the larger Herpevac study in women only.

In the Herpevac study, however, the investigational vaccine was ineffective in protecting against genital herpes disease. The estimate of vaccine effectiveness was 20 percent, but all estimates have statistical uncertainty, and this effect was not substantially different from zero.

It is not known at this time why the vaccine proved ineffective, but the study collaborators continue to evaluate the trial data and intend to provide a more detailed analysis at a later date.

All the study investigators have been informed of the results. Study participants are being notified as to which vaccine they received, and those volunteers who received the candidate herpes vaccine are being offered Havrix.
HSV-1 and HSV-2, which cause cold sores and genital herpes disease, may be transmitted through sexual or other skin-to-skin contact, and can be spread even when the infected individual shows no symptoms. HSV can cause severe illness in infants born to HSV-infected women, and the virus has been identified as a risk factor for HIV transmission in adults. An estimated 1 in 4 women in the United States has genital herpes.


Less Than Half of Essential Workers Willing to Report to Work During a Serious Pandemic, Study Finds

ScienceDaily (Sep. 30, 2010) — Although first responders willingly put themselves in harm’s way during disasters, new research indicates that they may not be as willing—if the disaster is a potentially lethal pandemic.

In a recent study, researchers at Columbia University's Mailman School of Public Health found that more than 50% of the first responders and other essential workers they surveyed might be absent from work during a serious pandemic, even if they were healthy.

The study, reported online in the October issue of the *Journal of Occupational and Environmental Medicine*, involved over 1100 workers recruited from six essential workgroups, all located in the New York metropolitan area. The workgroups included hospital employees, police and fire department personnel, emergency medical services workers, public health workers, and correctional facility officers.

The researchers found that while 80% of the workers would be able (i.e., available) to report to duty, only 65% were willing. Taken together, less than 50% of these key workers were both willing and able to report to duty. According to the lead author, Dr. Robyn Gershon, Professor of Clinical Sociomedical Sciences and Associate Dean for Research Resources at Columbia University's Mailman School of Public Health, and Faculty Affiliate at Columbia University's National Center for Disaster Preparedness, "these data indicate that non-illness related shortfalls among essential workers could be substantial."

In anonymous surveys, workers reported on their willingness to work during a serious pandemic; the percent willing ranged from a high of 74% (public health workers) to a low of 56% (correctional workers). The researchers found that motivation to work during a serious pandemic was associated with workplace safety measures and trust in the employer’s ability to protect workers from harm. Workers were also more willing to report to duty if their employer provided them with respirators and pandemic vaccine and had an established pandemic plan. Willingness was also tied to past experience; essential workers who had responded to a previous disaster were significantly more willing to report during a pandemic.

The researchers found that workers’ ability or availability to work during a serious pandemic was closely linked to their personal obligations. Referred to as “dilemmas of loyalty,” otherwise healthy essential workers might stay at home to care for sick family members or their children—if schools are closed. Organizational policies and programs that help workers meet their personal obligations will also increase workers' ability to work. "Even something as simple as ensuring that workers can communicate with their families while they are on duty, can have a big impact on both ability and willingness," reports Dr. Gershon.

Even though the Centers for Disease Control and Prevention (CDC) made workplace pandemic planning and training materials readily available, the Columbia study did not find much evidence of preparedness. Only a small proportion of the workers (9%) were aware of their organization’s pandemic plans, and only 15% had ever received pandemic influenza training at work. As Dr. Gershon notes, “the study findings suggest that these preparedness steps are important in building worker trust. Workers who trust that their employers can protect them during a communicable disease outbreak will be significantly more likely to come to work and perform their jobs—jobs that are vital to the safety, security and well-being of the entire community.”

To help ensure adequate staffing levels, employers should focus preparedness efforts on worker protection and the development of policies that facilitate the attendance of healthy workers. The authors suggest a number of relatively straightforward strategies that employers can take to support employees’ response during pandemic outbreaks. These include:

- Prepare a plan to quickly and easily vaccinate essential workers and their families, so that when a vaccine is available it can be readily distributed.
- Discuss respiratory protection needs with public health officials. They can provide guidance on the need, feasibility, and use of these safety devices.
Guidance on planning is available from CDC-funded Preparedness and Emergency Response Learning Centers, such as the one at Columbia University’s National Center for Disaster Preparedness.

**Journal Reference:**
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